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# Endocrinology

*The* Bulletin *of the*
Association *for the* Study *of*

# Internal Secretions

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Manuscripts of three types of original work are desired for publication:

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## THIS NUMBER AND THE NEXT

In this number we are presenting to you the fourth of a series of papers prepared by Drs. Rowe and Lawrence of Boston, two of the interesting papers read at the Minneapolis meeting and two other papers of equal interest.

We have on hand for the final number of this volume the following:

Studies of the Endocrine Glands. VI. The Pluriglandular Syndromes. Allan Winter Rowe and Charles Henry Lawrence, Boston.

The Thyroid Gland in Infections; the Effect upon the Basal Metabolic Rate. N. A. Womack, W. H. Cole and A. G. Heideman, of St. Louis.

Ovarian and Placental Hormone Effects in Normal, Immature, Albino Rats. George T. Golding and F. T. Ramirez, Columbia, Mo.

The Influence of Pineal Feeding upon the Rate of Metamorphosis in Frog. John Addair and F. E. Chidester, Morgantown, West Va.

A case of Diabetes, Refractory to Insulin, with Hyperplastic and Adenomatous Adrenals. R. A. Moore, Columbus.

The Vaginal Smear Method of Assay of the Ovarian Hormone. Lydia C. Kahnt and Edward A. Doisy, St. Louis.

The Distribution of the Ovarian Hormone between Liquor Folliculi and the Residual Tissue. Sidney Thayer and Edward A. Doisy, St. Louis.

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## OUR NEXT ANNUAL MEETING

Arrangements have been completed for the holding of our next annual meeting, Tuesday, July 9, 1929, in The Auditorium, Portland, Oregon. More definite announcement of this will be made in a later issue of ENDOCRINOLOGY.

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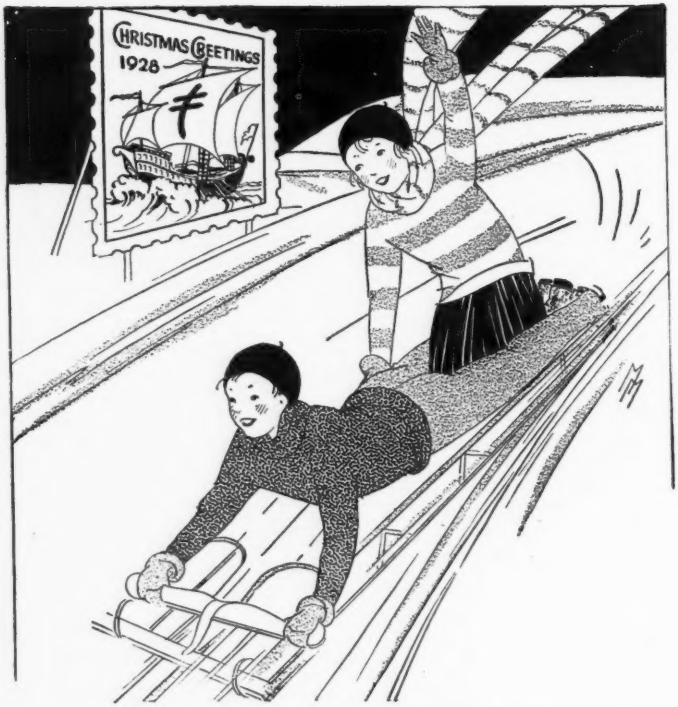


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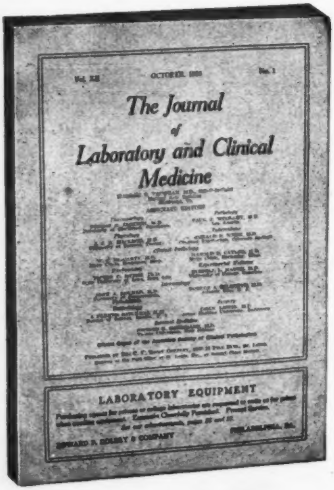


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September-October, 1928

# IODINE DEFICIENCY SYMPTOMS AND THEIR SIGNIFICANCE IN ANIMAL NUTRITION AND PATHOLOGY*

JOHN M. EVVARD, Ph. D.
Animal Husbandry Section
Laboratory, Iowa State College
AMES

## INTRODUCTION

### REVIEW OF IODINE LITERATURE AND OBSERVATIONS, WITH PARTICULAR REFERENCE TO DOMESTIC ANIMALS

Although the cause and treatment of goiter in animals has in comparatively recent years engaged the attention of breeders and scientific workers, the disease has masqueraded under many colors and in many lands since ancient times. Vegitius in the fourth century observed goiter in draft animals and the Berber explorer, Leo Africanus, wrote lucidly of the goitrous and cowardly lions common to certain regions in the Atlas Mountains of Morocco. The effect of goiter in these animals was so marked as to perpetuate the old proverb: "Thou art brave as a lion of Alga, whose tail may be eaten by calves."

In more modern times we find that losses due to this disease have apparently increased, proportionately speaking. Due to

*Delivered, Minneapolis, June 12, 1928, at Twelfth Annual Session, The Association for the Study of Internal Secretions.

modern developments in efficient sanitary control and prevention there has been a marked decrease in live stock losses because of parasites and infections. Hence diseases of different etiology have, to a considerable extent, been neglected. Today, however, many disorders having a distinctive nutritional basis are now enjoying the limelight. Now-a-days upwards of 60, 70 and in

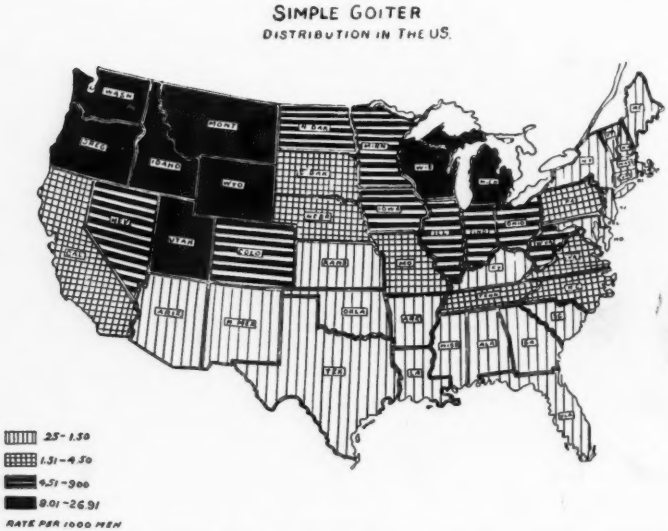


Fig. 1. Distribution of simple goiter in men—U. S. A. by states. (Drawn by us, based on World War Draft Board data of Davenport and Love, Sci. Mon., January, 1920.) In some states, as Illinois and Pennsylvania, the goitrous condition in swine and sheep is reported more frequently from the northern portions. Compare Fig. 2.

some cases even close to 100 per cent of the pigs and lamb death losses are averted in certain districts. Efficiency in feed utilization is likewise often attained through the feeding of small amounts of iodine.

It is unfortunate that many authorities in the animal production field are still emphasizing hairlessness and "big neck" of the new-born as sole and distinctive symptoms of goiter. Although we are thankful for such outstanding signs, many cases of iodine shortage, not so distinguished or recognized, are being

wrongly diagnosed, hence progress in the promotion of animal health is hindered.

### ETIOLOGY AND DISTRIBUTION OF GOITER

Stang and Wirth (1926) have pointed out that exophthalmic goiter does not normally occur in the lower animals; they further claim that it cannot be produced experimentally in an uncomplicated form. More important still, they emphasize that no cases have apparently been secured through the use of thyroid extract or the application of iodine feeding per os. These authors think that natural selection has probably eliminated the ordinary exophthalmic goiter from domestic animals, for in

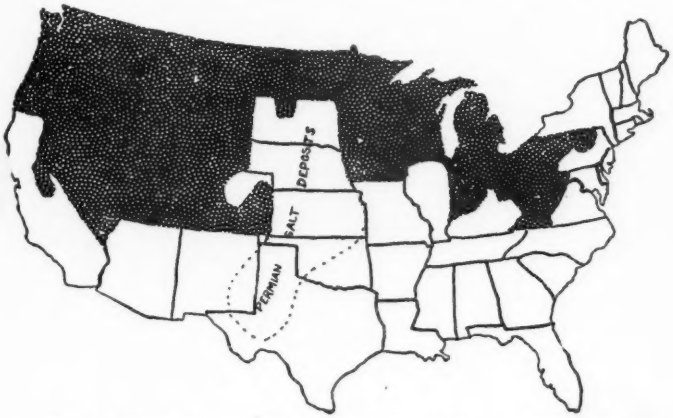


Fig. 2. Distribution of simple goiters in men U. S. A. geographically. Deduced from World War Draft Board data, courtesy McClendon, Hathaway and J. A. M. A. (May, 1924).

The area shown in black furnished soldiers every thousand of whom had from 5 to 111 men with goiters. A goiter in this case was defined as "too large to button a military collar around." Men showing slight goiter were passed and no record taken.

The Permain Salt Deposits shown in this figure were formed from the evaporation of sea water, which left extensive salt beds showing some iodine.

Compare Fig. 1, noting the general similarity. Fig. 1 shows four degrees of goiter prevalence; Fig. 2, goitrous and non-goitrous. The goitrous regions for domestic animals coincide, insofar as our observations go, with the human findings.

publications up to 1922 only 9 clinical cases were noted: 3 in horses, 2 in cattle and 4 in dogs. In 1923, a Basedow goiter was reported by Joest in sheep, but as yet no cases of hyperthyroidism have been reported in swine. On the other hand we have numerous reports of endemic goiters and cretinism in farm animals.

In North America, important foci for goiter are in the St. Lawrence river valley and Great Lakes basin where large numbers of lambs, pigs and dogs may be affected. In the Northern Plains region, extending westward from the Great Lakes to the Rockies on both sides of the International boundary, new-born pigs, lambs and other animals are especially subject to goiter; oftentimes, following winters of heavy snow, a large percentage of the spring pig crop is born hairless. The goitrous condition, however, is more often sporadic than endemic. Finally, one of the most important endemic areas is the Pacific Northwest, especially in Oregon, Washington, Montana, Alberta and British Columbia. In certain intermountain valley sections it has been

Fig. 3. Hairless pig from state of Washington (close view). Note signs of weakness—droopy eyelids, unstable balancing and extended position of front toes.

well nigh impossible successfully to raise young stock of any domestic species because of the incidence of marked thyroid hyperplasia.

## SYMPTOMS OF IODINE DEFICIENCY

The goitrous symptoms of pigs and lambs will receive major emphasis. In the iodine deficient territories represented by the Great Lakes basin and the Northern Plains area it is the pigs, goats and lambs which are the most likely to manifest gross pathology, easily observable.

Kalkus (1920) gives a very brief and satisfactory review of iodine deficiency symptoms in pigs and lambs. These are supplemented with our own observations in the development of the composite picture presented.

So-called hairlessness in new-born pigs, the result of thyroid hyperplasia, is a peculiar manifestation inasmuch as the alopecia

in the litters is rarely complete, many stages being represented within one litter; less frequently does the whole litter show complete baldness. Then, too, sows which are litter mates and have received similar care may farrow dissimilar litters, one showing hairlessness, and the other exhibiting, on casual observation, apparently normal pigs.

Pigs with alopecia adnata are generally born alive but the great majority die within a few hours. A very few may live and after several weeks become, superficially speaking, apparently normal. Affected pigs, farrowed alive, always show weakness and loss of vitality, seemingly in proportion to the degree of hairlessness. If entirely bald, they usually lie on their sides

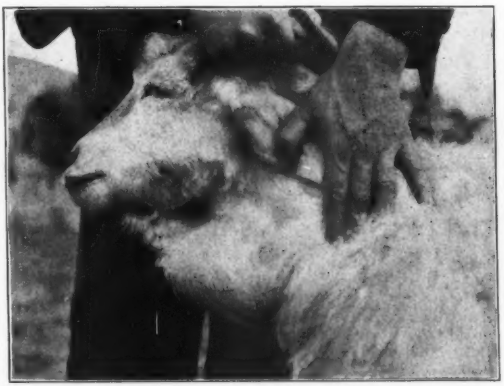

Fig. 4. A goitrous nanny goat from Pacific Northwest.

unable to get onto their feet to suckle. If disturbed they squeal complainingly, in a peculiarly "dejected" and suppressed manner.

The skin of these pigs is thickened, pulpy and very tender. Bruises develop a livid red color, due to congestion and hemorrhage, and rarely do they heal satisfactorily. The pigs are in most instances seemingly quite fat (apparently adematous), often of good size and are generally carried in utero somewhat longer than normal.

Autopsies generally, although not invariably, reveal thyroid enlargements. Kalkus reports the average weight of thyroids

as 646.6 mgm. for normal pigs, although an abnormal pig may have glands weighing only 200 mgm. compared to a weight as much as 380 mgm. for normal thyroids. In no instance was the thyroid gland of pigs sufficiently large to be externally observable.

Histologically, the thyroid change in hairlessness is not always easily recognized. At times colloid material may be observed, but generally there is a degeneracy showing widely separated and irregular tubules with the intercellular spaces filled with serum, leucocytes, fibroblasts, extravasated blood and exfoliated follicle or acinic cells. Even these symptoms are sometimes absent. Other organs, too, may be affected, more often the heart, which seems to be dilated with a fatty degeneracy

Fig. 5. A group of goitrous kids, showing mohairlessness, from Pacific Northwest.

of the muscular tissue. Less often hemorrhages are present in the kidneys, intestines and heart, and serum accumulations in the thoracic and abdominal cavities.

The thyroid glands in sows farrowing hairless pigs are usually enlarged, oftentimes greatly so. Hart and Steenbock (1918) found the abnormal thyroid gland of a 300-pound sow to be the size of a man's fist, much larger than the "walnut-sized" normal gland. The iodine content of affected glands is practically always much below that of normal glands.

Alopecia adnata is not a universal symptom of iodine defi-

ciency. Oftentimes the pigs may be completely though thinly haired, and quite strong at birth. Yet such pigs often develop iodine deficiency symptoms shortly after farrowing. In many cases, the diseased condition is accompanied with manifestations of diarrhoea (scours), loss of appetite, slow growth, roughness of coat and other untoward symptoms.

The feeding of iodine carriers to the sows (which presumably transfer some of the iodine to the milk), or directly to the pigs, often brings about a slow return to normality.

At times, however, congenital cretinism may appear, in which case the pigs, although farrowed apparently normal, rapidly become cachetic even though they suckle with eagerness. If such pigs live they are most likely to become mis-shapen, ugly

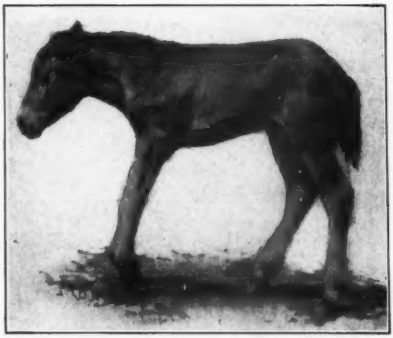

Fig. 6. A goitrous foal, showing contraction of flexor tendons in forelegs. Note lowered head position, a sign of weakness.

and oldish in appearance, very rarely attaining normal weights. Iodine therapy seldom if ever corrects the malady, although recoveries have been reported to us, following continued feeding of small dosages of desiccated thyroid gland. In such cases we suggest the experimental use of iodide and desiccated thyroid administration to the sows during pregnancy. Cretinism in swine should, however, be considered with an open mind until it is more completely investigated under carefully controlled conditions.

In the experience of Kalkus (1920) with lambs born in the State of Washington, in markedly goitrous regions, the affected glands are not generally large enough to be externally

discernable, although we have observed glands as large as an orange with smaller ones the size of hens' eggs. Glands as large as these are, in his observations, comparatively rare. The lambs may or may not be wool-less, the former condition being comparatively infrequent. Wool-less lambs rarely live long.

The observation of Kalkus in regard to the size of the affected thyroids in lambs is contrary to our experience in the Middle West. It may be that the breed of sheep is a factor inasmuch as certain characteristics of fine wooled breeds (Merinos and Rambouillets), with heavy skin wrinkles and protruding wool in the cervical region, hide or mask the thyroid

Fig. 7. Weak, goitrous foal in recumbent position. Note relative inability to raise head, drooping ears and eyelids and extended rear legs.

hyperplasia. Then, too, there is the possibility that some breeds may require less iodine for normal metabolism than others. In new-born Hampshire lambs we have frequently observed large goiters, but this breed is remarkably free from wrinkles of loose skin at the neck.

Histologically, the enlarged glands show small amounts of colloidal material or none. In marked hyperplasia the glands are in some cases very soft. In the degenerated gland one may find exfoliated columnar epithelial cells in the lumina, smaller lumina, and unevenly sized follicles.

The percentage of iodine content in the affected glands is generally much below that of normal glands, but the proportion of the iodine present does not necessarily decrease as the weight of the gland lessens. Changes in other organs are very similar

to that reported as found sometimes in pigs, namely, dilation of heart and hemorrhagic areas—notably on the kidneys, liver, pericardium and in lymph nodes. Extensive edema is oftentimes noted in the subcutaneous tissues.

Goats are affected in much the same way as sheep, but the goiters are usually larger.

Fig. 8. Goitrous calf with apparently healthy mother from province of Alberta, Canada. Note the goiter in the well-haired calf. Autopsy on mother would probably reveal a damaged thyroid.

Kalkus also reports many cases of goiter in both adult horses and new-born colts. On certain ranges from 30 to 50 per cent of all adult horses had visibly enlarged thyroid glands. These animals did not seem to be inconvenienced in any way insofar as their general health was concerned. In the new-born foal, however, the goitrous condition was extremely fatal. The affected colts were usually born alive, being well developed in physical body. From 75 to 90 per cent of the colts may be affected, and approximately 95 per cent of such animals are either still-born or die shortly after birth.

In most instances when seen in the recumbent position they

appear normal, although in some cases the lack of vitality is easily discernable even in this position inasmuch as the foal rests its nose on the ground with eyes half closed and ears drooping. The hind legs are extended, instead of lying forward underneath the body. However, when the colt attempts to rise marked weakness is observed. They are rarely able to stand unassisted because of a decided contraction of the flexor tendons in the fore legs, which causes a knuckling-over. An extension of the flexors of the hind legs was likewise observed. This latter condition causes the animal to stand on the posterior part of the fetlocks.

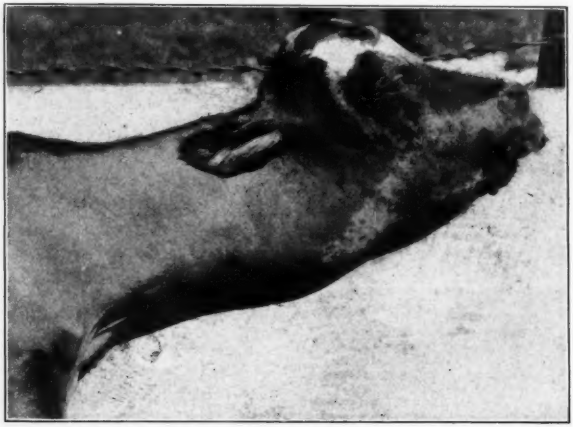

Fig. 9. Calf with gross goiter from Pacific Northwest. Note partial alopecia and droopy eyelid.

The breathing may or may not be labored. The badly affected animals usually live from one to three days, gradually becoming weaker until death relieves without a struggle.

A careful autopsy of four weak colts did not reveal marked enlargement of the thyroids. In three of the colts the enlargements were so slight as to be hardly discernable, and in the fourth instance the thyroids were approximately as large as hens' eggs.

Very few changes were noted in other organs. Although all cases showed contractions of the flexors in the fore legs and

extension of the same in the hind legs, the bones were apparently normal.

Goitrous calves are also prevalent in some districts. The calves are weak, and oftentimes show "big-necks." Autopsies reveal changes quite similar to those noted for lambs.

Kernkamp (1925) reports several instances of goiter in poultry. As yet only a very few cases have been observed. The affected birds were not suspected of being goitrous until dressed for the table, when the enlarged thyroids were noted. Histologically the thyroids presented enlarged acini filled with colloidal material.

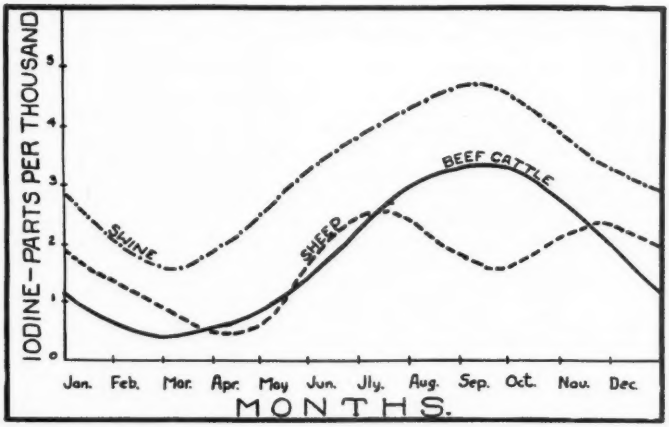


Fig. 10. Chart showing iodine, by months, in thyroids from Chicago slaughtered sheep. (Drawn and adapted by us from data of F. Fenger, Jour. Biol. Chem. 13:1913.)

Note correlation between grazing time on pasture in summer season and iodine content; the glands store iodine when animals graze. Note dip in sheep beginning July; our interpretation of this decline is that a relatively larger proportion of sheep arrivals in Chicago, July to October, come from the iodine deficient or goitrous states of Nevada, Idaho, Oregon, Washington, Montana, and Utah. These curves suggest that if dessicated glands of high iodine content are desired for therapeutic use that, at Chicago, swine or beef cattle thyroids should be selected in August, September and October, and sheep ones in July and perhaps in December.

## SOURCES OF IODINE IN NATURE

This topic has been handled so ably and fully by many investigators—McClendon, Marine, Forbes, Von Fellenberg and others, that we shall limit our discussion mainly to a correlation of their findings with common farm practices.

If added dosages of iodine compounds are not fed to animals, the degree of iodine deficiency, if any, depends on the iodine content of natural feed stuffs, including water. In the case of animals which consume more or less dirt, as do swine in their rooting and herbivora in their grazing, the composition of the soil is a factor. The previous store of iodine in the body bears on the problem of deficiency.

The quantitative content of iodine in natural feed stuffs varies markedly. In general, the country may be divided into three regions: The region of sufficient iodine resources, extend-

Fig. 11. Salt is a good iodine carrier for efficient administration. All classes of livestock, particularly herbivora, take readily to salt in fairly regular fashion, hence by mixing the iodide with this essential nutritive substance the chances of regular ingestion are extremely favorable.

ing southward along the Eastern Appalachian slope across the Southern prairie belt to the Pacific coast. The semi-sufficient area confined to the east Central and Middle-western states excepting the areas immediately surrounding the Great Lakes basin. Finally, the territory of inadequate iodine supply elsewhere identified in this paper as an area of endemic goiter.

Losses due to goiter in the area of sufficient iodine supply are apparently very small. The abundancy of iodine may be assigned to a heavy rainfall and closeness to the ocean. Iodine is universally found in nature; due to the vaporizing property of this element there is a persistent evaporation of iodine from the ground to the atmosphere and with the precipitation of rain and snow this atmospheric iodine is again carried to the ground and perhaps to the sea. Regions near the ocean which have a relatively abundant rainfall are more apt to retain their iodine resources. On the other hand, certain inland areas with only a

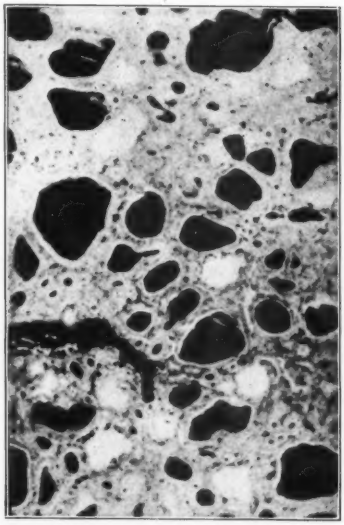

Fig. 12. Thyroid of normal swine. Note uniform follicular distribution; also colloid in follicles. (X125.)

small annual rainfall and a long distance from the ocean soon, geologically speaking, lose their natural iodine store. When evaporation exceeds the rainfall, particularly when the precipitation is heavy and the drainage light, the iodine stores in the soil are likely to be relatively high.

The area with a relative abundance of iodine has a temperate climate allowing extensive grazing by all classes of animals. This tends to promote the ingestion of a bulky herbaceous

ration having a relatively high iodine content. Possibly, too, the animals drink muddy water, thereby increasing the iodine storage.

In the endemic areas of the North most of the trouble is with the young born early in the spring. The dams have usually been on a restricted dried fodder and grain (sometimes) ration or a sole ration of concentrates, the latter being the case with many sows. Deep snows and frozen ground discourage ranging and dirt eating; and clear well water is usually the sole drink. Under these circumstances the ingestion of "natural" iodine is at a minimum level. Very often stockmen have empirically determined that a month or two of grazing on a luxuriant forage before the birth of lambs, pigs, kids, or colts tends markedly to reduce goiter losses.

McClendon (1927) reports numerous analyses covering the iodine content of feeding stuffs and water. The following tabulation indicates the iodine content of feeds from goitrous and non-goitrous regions.

| | *Iodine, Parts per Billion* | |
|---|---|---|
| *The Feed* | *Goitrous Region* | *Non-Goitrous Region* |
| Wheat | 6.6 (Minn.) | 9.3 (Me.) |
| | 1.0 (Minn.) | |
| Oats | 10.0 (Minn.) | 23.0 (Conn.) |
| | | 175.0 (Me.) |
| Carrots | 2.3 (Ore.) | 170.0 (Cal.) |
| Water | .01 (Minn.) | .60 (Va.) |
| | (Wash.) | 1.10 (N. Y.) |
| | .012 (Iowa) | 2.50 (N. Y.) |
| | .14 (Minn.) | 3.20 (Ga.) |

Sea foods are unusually good natural sources of iodine. Among these cod liver oil, which contains from 4000 to 6000 parts per billion, is becoming of increasing importance in farm animal feeding.

Domestic animals raised in the region of rich "natural" iodine resources probably do not require mineral iodine supplementation in order to insure satisfactory metabolism. On the other hand, economic losses are likely to be imminent with animals raised in other sections of the country unless iodine additions are incorporated in the ration, especially during the winter and in the pregnancy period.

THE METABOLIC EFFECT OF THYROID GLAND ACTION

We are well aware that thyroid action is closely associated with metabolism, especially in heat production, with a consequent normal or abnormal consumption of nutritive principles. This action is well illustrated, unfortunately oftentimes too well, in the use of thyroid products for reducing purposes. Recently Abelin (1928) briefly summarized the present knowledge of the chemical action as follows: In the classical scheme of glycogen metabolism of the muscles, we may divide the metabolic process

Fig. 13. Thyroid of hairless, new-born pig. Note irregular tubules; also absence colloid; also presence of exfoliated follicle cells and blood extravasations. (X125.)

into the following three parts: (a) the primary splitting of the complex molecule into two simple compounds, (b) the partial oxidation of these compounds, (c) the resynthesis of these intermediary products into original cell protoplasm. In normal metabolism there is a sharp differentiation between the processes. With disordered thyroid action, however, there appears to be a deficient resynthesis of the metabolic products into the original cell material. Thus the carbohydrate material is not properly resynthesized into glycogen and hence the fats and proteins are not properly utilized. In general, the rate of basal metabolism is a mirror of the prevailing correlation between decomposition and resynthesis. Aron (1926) advances corroborating evidence

of probable importance when he reports that the beginning of the embryonic thyroid development synchronizes exactly with the development of the Islets of Langerhans of the pancreas. All species studied reacted alike.

Hunziker (1928) advances a new theory covering the iodine requirements of animals, basing his interpretations on the following data from Von Fellenberg:

IODINE CONTENT AND THYROID WEIGHTS OF VARIOUS BREEDS OF CATTLE

| Breed | No. animals | Average live weight, Kgm. | Ave. weight of thyroids per 100 Kgm. live weight, mgm. | Average iodine content per 100 Kgm. live weight, mgm. |
|---|---|---|---|---|
| Simmenthaler | 12 | 562.5 | 6.80 | 0.86 |
| Shorthorn | 5 | 510.0 | 8.00 | 1.60 |
| Braunvieh | 5 | 332.0 | 14.05 | 3.47 |
| Norweger | 4 | 314.0 | 17.70 | 2.36 |

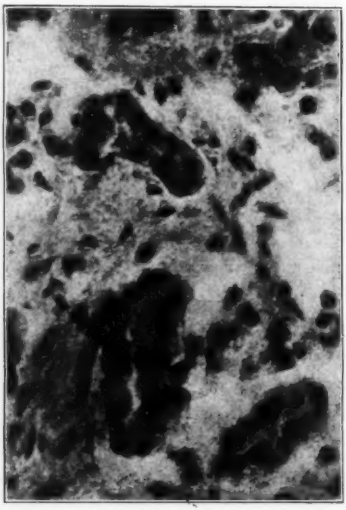

Fig. 14. Same as Fig. 13. Specimen magnified. (X500.)

He introduces substantially the following observations and conclusions: The heavier the average weight the smaller the thyroids and the lower the iodine per unit of live weight. The reason for this correlation probably lies in the effect of the thyroid extract on metabolism. Nevertheless metabolism, especially

the rate of metabolism, must be based essentially on the needs of the animals. This is primarily limited by the extent of the heat needs of the animals, which in turn is limited by the extent of the heat-radiating surface of the animal. The weight gain increases at a "cube" rate, while the corresponding surface area gain is at a "square"; therefore, if a close correlation (multiple, of course) is determined, covering mass, surface, thyroid weights and iodine content (thyroids), a good many enigmas may be cleared up.

Briefly, we may conclude that iodine and the thyroid glands

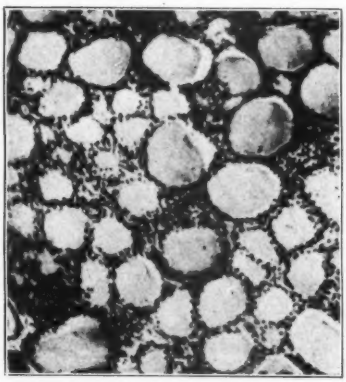

Fig. 15. Normal thyroid of a lamb. Note regularity of size and distribution of follicles filled with colloid, uniform cuboidal epithelium of follicles. (X125.)

play a fundamental and far reaching role in regulating the "metabolism rate" and especially in the economy of feed utilization. The latter premise will be developed more completely in a study of contemporary controlled feeding experiments with farm animals.

## IODINE FEEDING EXPERIMENTS

Although a number of instances are reported in the literature wherein the administration of iodine to pregnant animals has prevented the birth of goitrous new-born animals, only a very few carefully controlled experiments are reported giving quantitative as well as qualitative results.

Among the former Kalkus (1920) reports field trials in

which tincture of iodine was furnished to ranchmen in return for certain birth records. Twenty-five stockmen treated collectively 77 mares, 137 cows, 28 sows and 66 sheep. In no case were goitrous young produced, although the same stockmen had previously suffered considerable losses due to goiter.

Hart and Steenbock (1918) report the feeding of 10 grams of potassium iodide per 100 pounds of a balanced basal ration to a sow which had previously farrowed three litters of hairless pigs on a similar or nearly similar ration without any incor-

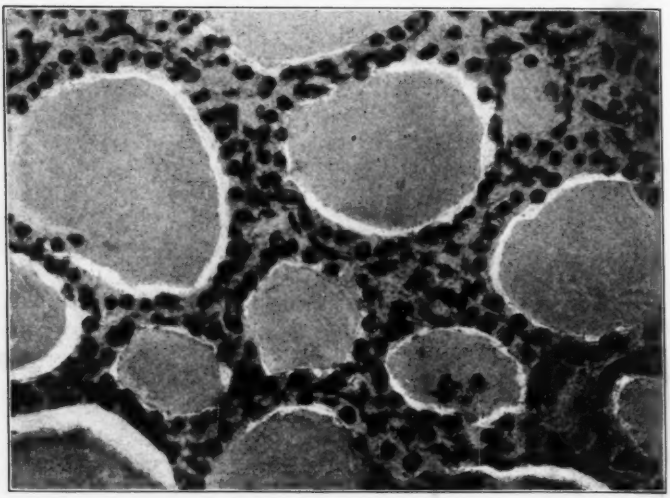

Fig. 16. Same as Fig. 15. Specimen magnified. (X500.)

porated iodide. The fourth litter appeared to be normal in every respect. This evidence indicates that iodine therapy prevented hairlessness.

As yet we know relatively little, from the standpoint of controlled experimentation, as to the preferable form and amount of iodine that should be fed. However, at the Iowa Agricultural Experiment Station we have had good results feeding potassium iodide in amounts equal to 0.00023 grain daily per pound of sow instead of the 0.00308 grain daily which Hart and Steenbock fed in the average sow's ration. The quantitative necessity of the added iodide is of course largely dependent on

the amount of iodine carried in the basal ration. Hansson (1927) reports European stockmen as feeding up to 0.00771 grain daily per pound live weight, although he recommends—based on Von Fellenberg's findings—a much smaller amount for maintenance, namely, about 0.00003 grain, plus additions to be regulated according to the specific nature of the production.

A rather closely controlled experiment has recently been reported by Weiser and Zaitschek (1927) who fed two comparable groups of sows a similar basal organic and mineral ration with the exception of a potassium iodide allowance to

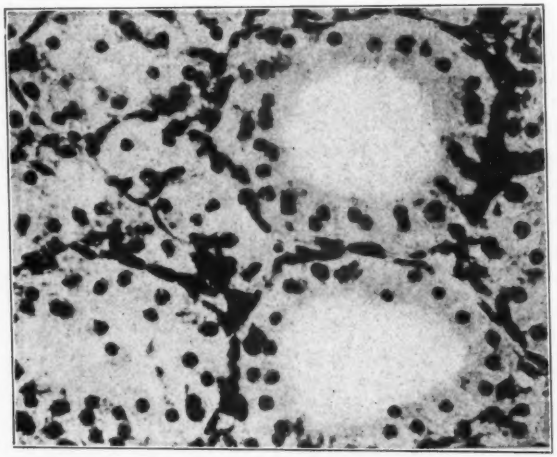

Fig. 17. Thyroid of goitrous lamb. Note absence of colloid, desquamation and columnar epithelium lining of uneven follicles. (X500.)

one group. During the last three weeks of gestation and also during the suckling period the sows, which were to farrow late in November and early in December, were fed a corn, barley meal and fish meal ration (changed somewhat later in the period). To the check group, I, was fed 50 grams (about 0.1 pound) calcium carbonate daily per sow. The other group, II, received the same mineral allowance except that it contained 0.25 percent potassium iodide (125 milligrams daily or about 0.0139 grain per pound of sow daily). The vital statistics for the two groups during the farrowing and suckling periods are:

| | Group I Not fed iodide | Group II Fed iodide |
|---|---|---|
| No. of sows | 17 | 23 |
| Duration of gestation period, days | 116 | 114 |
| Number of pigs per litter, average | 8.94 | 9.13 |
| Average birth weight per pig, lbs. | 2.82 | 2.55 |
| Total number of pigs | 152 | 210 |
| Born dead, percent | 0.66 | 2.85 |
| Smothered, percent | 2.63 | 11.45 |
| Died of disease, percent | 54.61 | 2.85 |
| Weaned, percent | 42.10 | 82.85 |
| Average weight of pigs, lbs.: | | |
| At birth | 2.82 | 2.55 |
| At 4 weeks | 11.64 | 12.87 |
| At 6 to 7 weeks | 15.22 | 23.10 |
| At weaning time (10 weeks) | 28.97 | 40.79 |
| Minimum | 19.80 | 26.40 |
| Maximum | 34.56 | 55.37 |

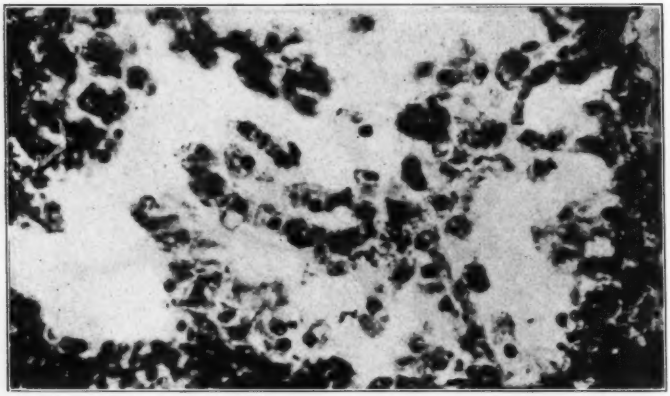

Fig. 18. Thyroid of another goitrous lamb. Note exfoliated cells in abnormal single follicle. (X500.)

These data show that even in so short a time as three weeks before farrowing enhanced results were gotten by feeding iodine. Note particularly the difference in the percentage of pigs weaned, namely, 42.10 for the non-iodide fed sows and 82.85 for iodide fed sows. Also note the "quicker" gain in weight, the final weight being nearly 41 percent in favor of the iodide fed pigs at ten weeks of age.

These investigators also fed the iodized calcium carbonate to a group of 50 pigs farrowed in early October. These pigs had been making subnormal growth and were rapidly dying in

spite of conscientious care. The selections were made after weaning and they were then placed on the basal ration plus iodide. In less than ten days the death losses stopped and the remaining pigs quickly regained their appetite and health, so much so that in a very short time they appeared normal in every way.

Kalkus (1920) has also reported a pertinent experiment in the control of goiter in goats. The tabulated results are as follows:

RESULTS OF IODINE TEST, 1917-18
(6 Does in Each Lot)

| Lot | Form of Iodine Compound | Dosage | Frequency and Method of Administration | No. of Young Born | Condition of Young at Birth |
|---|---|---|---|---|---|
| I | None | ..... | ..... | 10 | All hairless<br>8 still born<br>2 died shortly |
| II | KI | 2 grains in ½ oz. water | Daily during gestation period, per orem | 5 | All normal |
| III | Tincture of Iodine | 5 mils. of 10% sol. | Weekly during gestation, subcutaneous | 7 | All normal |
| IV | Tincture of Iodine | 1 mil. | Weekly during gestation, on back | 8 | 7 normal<br>1 slight thyroid enlargement, but well haired |

These results indicate that the method of application is of minor importance in the prevention of major gross symptoms.

Bowstead (1925) reported an experiment carried on in the Province of Alberta, Canada, in which two lots of pregnant ewes were fed a similar basal ration with and without potassium iodide. A third group had lime added, but without iodide. The daily basal ration per sheep consisted of approximately 3.3 pounds of oat hay, 0.3 pound of barley grain and self-fed salt. The potassium iodide was allowed with the salt, the mixture consisting of five ounces of iodide to each 100 pounds of salt.

The check group of ewes lost 25 pounds per head on the average during the pregnancy period and 83 per cent of the lambs showed goitrous symptoms, partial wool-lessness being observed. The group receiving the potassium iodide addition lost only 17 pounds per individual on the average and none of the new-born lambs showed any gross symptoms of goiter. Small additions of lime without potassium iodide were without curative properties inasmuch as 92 per cent of the lambs from this group of ewes showed goiters. The lime addition, however, improved

the nutritive qualities of the ration in that the average ewe lost but 7 pounds in weight.

In the summary of the experimental results, Bowstead emphasizes that the feeding of potassium iodide resulted in almost 100 per cent strong and thrifty lambs. These averaged about one pound (nearly 12 per cent) heavier than those of the two groups not fed iodide.

### THE EXPERIMENTAL FEEDING OF IODIDE TO SWINE

The positive results secured from the feeding of iodine to pregnant swine in the prevention of hairless pigs and allied con-

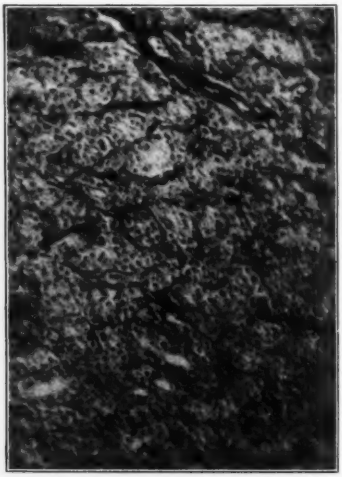

Fig. 19. Thyroid of goitrous new-born foal. Note numerous small tubules and colloid absence. (X125.)

ditions are outstanding. Alopecia adnata in the young swine is now being widely prevented when the cause is of nutritional origin, this by the feeding of an iodine carrier. To infer, however, that an iodine deficiency is not being experienced in swine herds if hairless or semi-haired new-born pigs are not evidenced is illogical. Well-haired pigs may, in our judgment, be the rule at farrowing time, and yet there may be an insufficiency of iodine for normal metabolism.

It is unfortunate from the standpoint of veterinary and farm practice that it is so difficult to detect enlarged thyroids or simple goiters in swine. In the present state of our knowledge we do not have any practical way of knowing exactly whether or not any specific farm is laboring, from the swine standpoint, under iodine deficiency. However, if the farm under inspection is in a goitrous or semi-goitrous area, or if goitrous conditions have been noted in other types of stock, it is pretty good policy to resort to iodine feeding as a matter of sensible insurance protection.

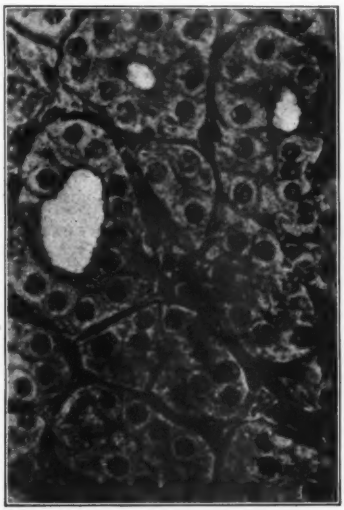

Fig. 20. Same as Fig. 19. Specimen highly magnified. (X500.)

In the experimental swine herds at the Iowa Agricultural Experiment Station we have never had, in the eighteen years of the author's experience, any hairless pigs at farrowing time which could be attributed to iodine deficiency. On the other hand, goiter has been experienced frequently in the new-born lambs of the breeding flock. The latter fact indicated that there might be an iodine deficiency prevalent in the swine herd. We inaugurated experiments in order to determine if the addition of iodide to ordinary rations fed to swine on grass or in winter

dry lots would yield favorable results, physiologically and economically speaking.

### FEEDING IODINE TO GROWING SWINE PROVES BENEFICIAL

In Table I are presented some results secured in three years of experimentation with young, growing pigs, fed with and without iodide additions to the basal rations.

The experiment was conducted on rape pasture. The basal ration fed was a standard one composed of corn grain, mostly yellow, "60 per cent protein" meat meal tankage, corn gluten meal, corn oil cake meal, linseed oilmeal, cottonseed meal, bone meal, and flake salt. This was full-fed to Group A in Experiment I. Group B, in the same experiment, was fed exactly the same, with the exception that a small allowance of potassium iodide was made, the iodide being mixed with the basal feed.

Fig. 21. Normal thyroid of cow. Note regularity of follicles and presence of colloid.

The growing and fattening swine on experiment showed no external evidence of iodine deficiency insofar as visual observation for specific abnormalities was concerned. However, Group B gained practically 8 per cent more rapidly and took 55 pounds less feed for the hundredweight of gain produced.

In Experiment II the basal ration was changed somewhat, consisting of corn grain, mostly yellow, cottonseed meal, blood meal, "high calcium" limestone, bone meal and flake salt. This was full-fed to Group A. Group B was fed the same excepting that potassium iodide was added. In this experiment we saw no gross signs of goiter even though careful observations were again made. Nevertheless, the iodide fed pigs gained more rapidly, practically 9 per cent more, and the feed requirement was close to 10 per cent less, 40 pounds below the check group.

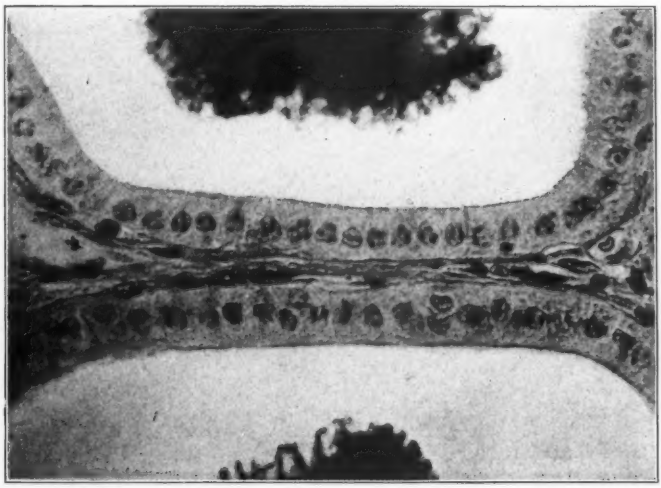

Fig. 22. Same as Fig. 21. Specimen highly magnified. Note the orderly, artistic biological architecture, and interfollicular elements. (X500.)

This experiment was conducted in the summer under pastureless conditions.

In a later year we again studied two groups of pigs under winter conditions. In this experiment the check ration consisted of eleven commonly used farm feeds. It was thought that the chances for iodine deficiency might be less if a wide variety of feeds were incorporated in the basal ration. Nevertheless, the results secured were similar to other years, the gains being faster, some 13 per cent more, and the feed requirements per hundredweight of avoirdupois produced on the pigs less, approxi-

## TABLE I

### FEEDING POTASSIUM IODIDE TO GROWING SWINE

Results of Three Experiments
One With and Two Without Green Forage
(Pigs Taken to Same Final Weight in Each Experiment)

| Experiment | Potassium Iodide Allowance per Pig Daily (Grains) | Green Leaved Forage Available | Year of Experiment | Season of Year | No. of Pigs Fed | Days Fed | Weight per Pig Initial Lbs. | Weight per Pig Final Lbs. | Average Daily Gain per Pig Lbs. | Average Daily Feed per Pig Lbs. | Feed Required for 100 Lbs. Gain (Omitting Forage) Lbs. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | | | | | | | | | | | |
| A | None | Rape | 1920 | Summer | 5 | 145 | 50 | 225 | 1.23 | 5.38 | 440 |
| B | 0.67 | Rape | 1920 | Summer | 5 | 133 | 50 | 225 | 1.33 | 5.11 | 385 |
| | Difference | | | | | 12 | | | 0.10 | 0.27 | 55 |
| II | | | | | | | | | | | |
| A | None | None | 1921 | Summer | 7 | 112 | 50 | 225 | 1.52 | 6.44 | 425 |
| B | 0.85 | None | 1921 | Summer | 7 | 103 | 50 | 225 | 1.65 | 6.37 | 385 |
| | Difference | | | | | 9 | | | 0.13 | 0.07 | 40 |
| III | | | | | | | | | | | |
| A | None | None | 1923-24 | Winter | 6 | 170 | 67 | 300 | 1.37 | 6.67 | 485 |
| B | 0.08 | None | 1923-24 | Winter | 6 | 150 | 67 | 300 | 1.55 | 6.93 | 446 |
| | Difference | | | | | 20 | | | 0.18 | 0.26 | 39 |
| Three-Year Average (straight) | | | | | | | | | | | |
| A | None | | | | 6 | 142 | 56 | 250 | 1.37 | 6.16 | 450 |
| B | 0.52 | | | | 6 | 129 | 56 | 250 | 1.51 | 6.14 | 405 |
| | Difference in Favor of Iodide | | | | | —13 | | | +0.14 | | —45 |

IODIDE FEEDING RESULTED IN 10% greater daily gain and 10% saving in feed.

mately 8 per cent. In this experiment no gross signs of a goitrous condition were noted.

The three year average showed that when a small amount of potassium iodide, from 0.08 to 0.67 grain of potassium iodide per pig daily, was fed the animals made 10 percent greater daily gains with a resultant saving of 10 per cent of the feed per unit of weight increase produced. Thus it may readily be seen that even under seemingly healthy conditions the controlled experi-

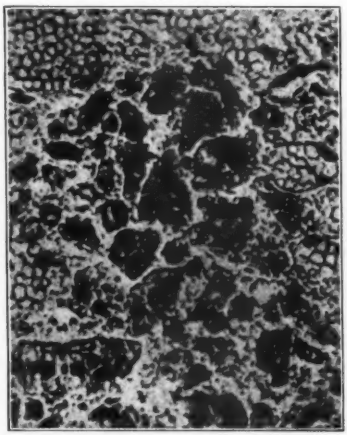

Fig. 25 Thyroid of new-born goitrous calf. Note disruption of follicles, connective tissue elements and extravasated, non-nucleated red blood corpuscles. (X500.)

ments revealed the fact that the addition of a small amount of iodide in the porcine rations increased the metabolism in a favorable manner, augmenting the gains and conserving the feed.

The greater growth evidenced by the iodide fed pigs was not only in weight but also in dimension. Careful measurements revealed the fact that, in Experiment II, the pigs grew longer and taller in the same period of time, when iodine was administered. The statistical interpretations of the data in these three experiments demonstrate quite conclusively that the results secured, with the differences in favor of iodide feeding, were significant.

EXPERIMENTS IN THE FEEDING OF IODINE TO SHEEP

In the spring of 1917 a number of new-born lambs, 23 out of 55 produced by 40 breeding ewes, showed noticeable enlargement of the thyroids. The ewes were fed in four groups, each group receiving a different ration. Every group produced goitrous new-born lambs. Fortunately, we had taken in the regular course of experimental procedure composite samples of the feeds used, and we found that iodine was present in only one of them. The rations fed were corn silage, timothy hay, oat straw, shelled corn, corn gluten feed and salt. Both the roughages and the grains were kept constant in quantity in each group fed.

The only feed carrying iodine was corn gluten feed; it containing 0.00011 percent. It is interesting to note whether or

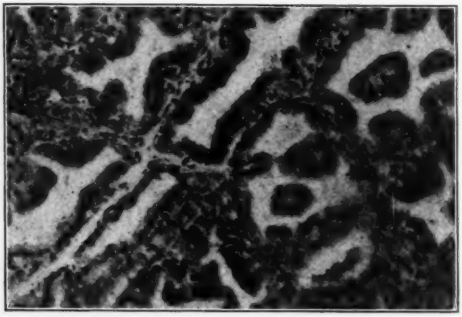

Fig. 24. Thyroid of goitrous calf six weeks old. Note absorption of blood extravasate, subsidence of congestion, new follicles in process of development and disrupted follicles. (X125.)

not its inclusion in increasing amounts in the daily ration per ewe protected against goiter to any extent. Two of the groups, receiving respectively ¼ and ½ pound of the corn gluten feed, the remainder of the pound grain allowance being shelled corn, per ewe daily, showed an average of 51 percent of the lambs affected with goiter, whereas the use of 1 pound of the same feed, no corn being given, in a corresponding group resulted in only 40 percent of goitrous lambs. The water which these ewes drank carried only 0.012 parts of iodine per billion, much

too low a proportion to be effective under such conditions of iodine shortage.

### ANOTHER CONTROLLED EXPERIMENT IN IODIDE FEEDING WITH PREGNANT EWES

A carefully conducted iodide feeding experiment was made in the winter of 1917-18 with the same breeding ewe flock which had given birth to so many goitrous lambs in the previous year. The ewes were divided into four groups of nine animals each. All ewes received the same basal ration, both quantitatively and qualitatively speaking. The daily ration per ewe of all groups

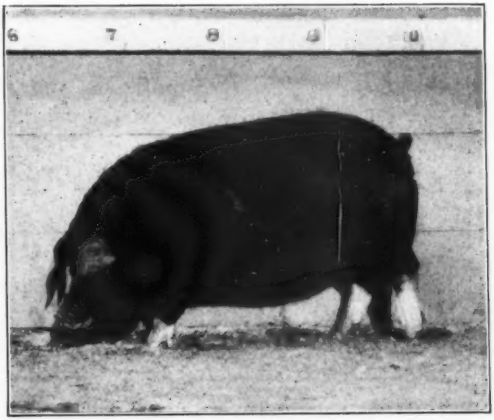

Fig. 25. Representative pig group A. Experiment II. No potassium iodide allowed. Compare Fig. 26.

was as follows: 0.25 pound shelled corn, 0.75 pound corn gluten feed, 2.00 pounds corn silage, 0.5 pound timothy hay, and 0.65 pound oat straw. All ewes were allowed to have access to iodine-free salt from the same source as that fed in the previous year when goitrous lambs were experienced in considerable number.

The daily dosage of potassium iodide per ewe daily was for the various groups as follows: Group A (check), none; Group B, 2.02 grains; Group C, 5.66 grains; and Group D, 6.09 grains. The dosages were purposely made large in order to find out if

any deleterious effects might result because of such liberal allowance. The iodide feeding covered a period of approximately two and one-half months during the pregnancy period.

No palpable goiter was observed in either the ewes or the young during the experiment, although the animals were examined frequently. Neither was iodism noted in any of the iodide-fed groups.

The same basal ration fed the previous year did not, however, protect against goiter, as we have hereinbefore shown. While the feeds fed were the same by name, the source was not

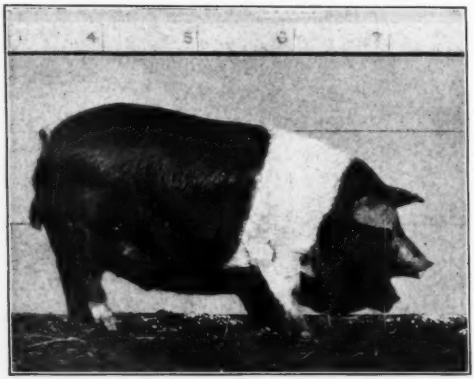

Fig. 26. Representative pig group B. Experiment II. Potassium iodide fed. Compare Fig. 25. Note sleeker coat and signs of more vigor.

identical with the previous year. We have found in this as well as through previous experience that feeds of the same kind may vary considerably in their iodine content even though produced under so-called similar conditions.

Some factor, more likely factors, as yet not understood alter the iodine content of the feed. Of course it is known that feeds produced in goitrous regions run on the average considerably lower in iodine than similar feeds, the products of goiter-free areas. Possibly such factors as the amount of rainfall, its distribution, the temperature, the character of the soil, and others may be thought of. The only way to be sure whether or not any one feed carries a sufficiency of iodine is to analyze it.

Table II carries data pertinent to our experimental inquiries; an interpretation of this table suggests the following:

1. There was very little difference in the average daily gain of the ewes in the various groups.

TABLE II

THE FEEDING OF EXCESSIVE DOSAGES OF KI TO PREGNANT EWES PROVES DETRIMENTAL TO LAMBS

Four Groups of 9 Ewes Each
Potassium Iodide Fed for Approximately 2½ Months
Winter, 1917-18

| Group No. | Potassium Iodide per Ewe Daily Grains | Average Daily Gain per Ewe Lbs. | New-Born Lambs Produced | Average Vigor of Lambs 100% = Perfect | LAMBS Dead at Birth % | LAMBS Dying Before Two Months Old % | LAMBS Total Deaths % |
|---|---|---|---|---|---|---|---|
| A | None | 0.19 | 14 | 90 | 0 | 7 | 7 |
| B | 2.02 | 0.22 | 14 | 74 | 0 | 43 | 43 |
| C | 5.66 | 0.18 | 15 | 60 | 20 | 60 | 80 |
| D | 6.09 | 0.23 | 13 | 48 | 23 | 69 | 92 |

2. The average vigor of the new-born lambs was affected adversely by the high dosages of iodide. As the doses increased

Fig. 27. Representative pig group A. Experiment III. No potassium iodide fed. Compare Fig. 28.

from 2 to 6 grains per ewe daily the average vigor, based on 100 per cent being perfect, decreased from 74 to 48 per cent. And the check group, not receiving added iodide, showed for the new-born lambs 90 percent of perfect vigor. Apparently, the heavy ingestion of potassium iodide was detrimental to the young in utero.

3. The number of dead lambs at birth was largest in Groups C and D, the ewes of which groups received approximately 6 grains of KI per head daily, the percentage being 20 and 23 percent respectively. On the other hand, when only 2 grains was administered there were no dead lambs at birth; neither did the check group show any.

4. The loss of lambs during the recorded portion of nursing period, two months, was much greater when the iodide ingested was the heaviest. The check group, A, showed only 7

Fig. 28. Representative pig group B. Experiment III. Potassium iodide fed. Compare Fig. 27. Note greater size and weight.

percent deaths, whereas Group D, receiving the heavy allowance of 6 grains of potassium iodide, showed 69 percent deaths.

5. Many of the deaths among the lambs during the suckling period were due to hemorrhagic septicemia; the causal bipolar organisms were identified by Dr. Charles Murray of the Veterinary Division of Iowa State College. Since all of the new-born lambs were kept in the same paddock, the iodide administration being discontinued at parturition time with the rations thereafter being kept on the same basis for all groups, it appears that the heavy administration of iodine in the form of potassium iodide decreased the resistance of the young to this specific disease.

Since the experiment was conducted in series fashion, increasing amounts of iodine being fed as the groups ranged from A to D, it is believed that the increased toll from the hemorrhagic septicemia was correlated with the size of the dosage of iodide. To make this more plain we emphasize that Group A receiving no iodide lost only 7 percent of its lambs, Group B receiving more iodide, or 2.02 grains per head daily, lost 43 percent of its lambs, Group C receiving 5.66 grains, 60 percent, and Group D getting 6.09 grains, 69 per cent during the recorded suckling period. Since the big proportion of the

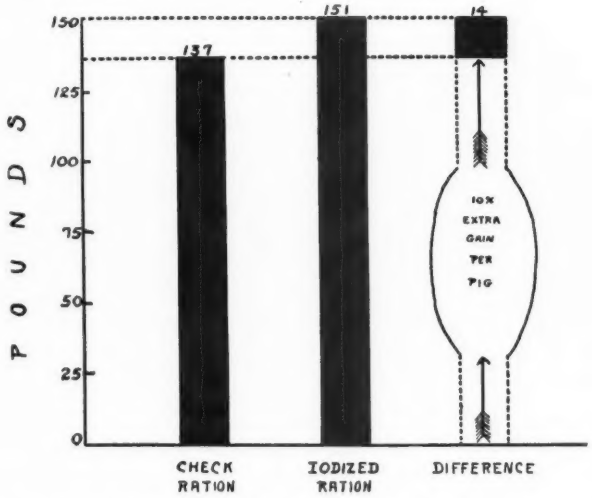


Fig. 29. Chart showing (graphically) relatively greater daily gain per pig of pigs fed potassium iodide in three experiments, I, II and III.

deaths occurred within two to six days after birth, we were suspicious that the milk of the ewes was altered by the iodide feeding, hence we made chemical examination to determine the facts. The results of these studies are given in Table III entitled "Iodine in Ewes' Milk Increased by Iodide Feeding."

6. Why did the heavy administration of iodide to pregnant ewes lessen the resistance of the new-born lambs to a certain disease? In the light of our latest experiments (see Tables IX and X, and discussion of them) it appears that dosages

of iodide during pregnancy in excess of the amount required for normal functioning of ewes and their new-born lambs decrease the size of the thyroids in the offspring, lower the amount of iodine per lamb thyroid and lessen the quantity of thyroidal iodine per unit of lamb weight. If marked successive excesses of iodide would further augment these trends, it may readily be seen that the thyroids of the new-born would become smaller and smaller, and further that the thyroidal iodine would diminish accordingly. Did such a process take place in the lambs of this experiment under discussion? Unfortunately, we did not study the thyroids of these lambs, so do not know. If such an atrophic and chemical change did take place, we might hypothe-

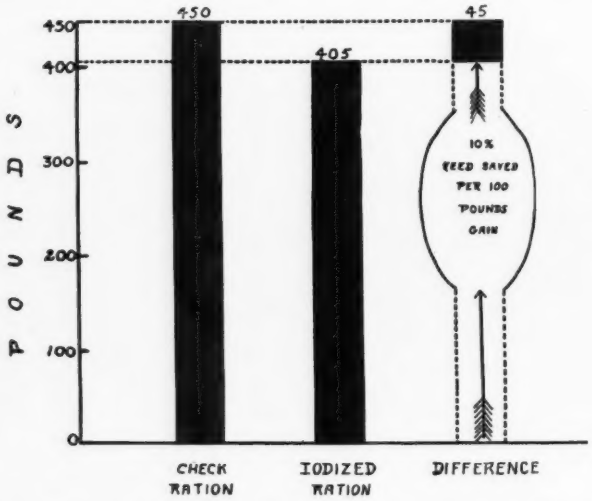


Fig. 30. Chart showing (graphically) relatively less average feed requirements per hundred-weight of increase made by the pigs fed potassium iodide in three experiments I, II and III.

size as regard the influence on the biological functioning of the thyroids of the unfortunate lambs stricken with hemorrhagic septicemia. Is it possible thus to reduce the thyroids of the lambs in utero and of the new-born in size and in iodine to the extent that they are injured severely enough that they do not function adequately in the protection of the organism? We shall proceed in future experimentation with new objectives in

mind, getting data that should throw light on the points involved in our questions.

TABLE III

IODINE IN EWES' MILK INCREASED BY IODIDE FEEDING
*Iodide Allowance Discontinued on Parturition Day*

| Group | Potassium Iodide per Ewe Daily (Grains) | Iodine in Milk Samples—Average —Colostrum— Samples | p.p.m.* | —Post-Parturition— 5 Days Samples | p.p.m. | 15 Days Samples | p.p.m. |
|---|---|---|---|---|---|---|---|
| A | none | 4 | 2.4 | 3 | 0.0 | 3 | 0.0 |
| B | 2.02 | 4 | 41.1 | 4 | 8.5 | 3 | 0.0 |
| C | 5.66 | 5 | 54.8 | 3 | 46.2 | 3 | 0.0 |
| D | 6.09 | 3 | 38.6 | 3 | 49.7 | 3 | 6.5 |

*Parts per million.

IODINE IN MILK OF EWES

As the amount of iodide increased in the ewes' ration, so, too, did the amount of iodine increase in the milk (see Table

Fig. 31. Gross observable goiter of new-born lamb typical of many observed in our experiments. Larger and smaller goiters were experienced by our lambs on iodine deficient rations. The lambs having the largest goiters were practically always quite weak and the mortality was extremely high. Rapid heart beat and dyspnea was noted. Very small goiters were not externally observable or palpable

III). The colostrum showed, in round numbers, 41, 55 and 39 parts of iodine per million parts of material, respectively, in the iodide-fed Groups B, C and D. Contrast these figures with 2.4, Group A, where no iodide was given.

Milk samples were again taken five days following parturition, with comparative results similar to those secured on the colostrum. The iodide feeding during the pregnancy period had its effect on the iodine content of these samples. After five days the milk from the check group showed no iodine, whereas the milk from Group D, 6 grains iodide allowance, showed 50 p.p.m.

At fifteen days the iodine had disappeared from the milk samples of Groups A, B, and C, but Group D, the heaviest iodide-fed group, still showed 6.5 p.p.m.

It is evident, therefore, that the lambs from the ewes heavily fed on iodide received extra liberal iodine supplies from their mothers' udders.

This experiment illustrates quite clearly the necessity of careful regulation of iodine feeding under some conditions; the evidence certainly points most suspiciously to the possible development of specific evil effects which may be experienced when too much potassium iodide is fed pregnant animals.

SUSCEPTIBILITY OF SEXES OF NEW-BORN LAMBS TO GOITER

We present in Table IV some data showing the occurrence of goiter, visually observable, in new-born lambs born in two different seasons—one quite goitrous, 1916-17, and another semi-goitrous, 1924-25.

It appears that the ewe lambs were more prone to this disease when the conditions of feeding and environment were similar. The data are too meager to warrant comment other than to state the facts, as has been done.

**TABLE IV**

GOITER DISTRIBUTION BY SEXES IN NEW-BORN LAMBS

Gross Goiters Observed

| | A Goitrous Season 1916-17 | | | A Semi-Goitrous Season 1924-25 | | |
|---|---|---|---|---|---|---|
| Observations | Rams | Ewes | Total Both Sexes | Rams | Ewes | Total Both Sexes |
| Sexes Distribution, total | 27 | 28 | 55 | 25 | 33 | 58 |
| *Large Goiters:* | | | | | | |
| Distribution, actual.. | 4 | 4 | 8 | 0.0 | 5 | 5 |
| Distribution, percentage of each sex or combination ..... | 14.8 | 14.3 | 14.5 | 0.0 | 15.2 | 8.6 |
| *Medium to small Goiters:* | | | | | | |
| Distribution,actual... | 7 | 8 | 15 | 0.0 | 1 | 1 |
| Distribution, percentage of each sex or combination ..... | 25.9 | 28.6 | 27.3 | 0.0 | 3.0 | 1.7 |
| Within the affected group..... | 46.7 | 53.3 | .... | 0.0 | 100.0 | ... |
| *Free from Goiter:* | | | | | | |
| Distribution, actual.. | 16 | 16 | 32 | 25 | 27 | 52 |
| Distribution, percentage of each sex or combination ..... | 59.3 | 57.1 | 58.2 | 100.0 | 81.8 | 89.7 |

## SHEEP FEEDING EXPERIMENTS CONTINUED—LATEST SERIES

In the fall of 1925 we inaugurated a series of experiments with ewes and their lambs, covering an indefinite period of time. To date, 1928, three years' work have been done and many data of an enlightening nature now grace our archives.

Four groups of ewes have been fed, under comparative and controlled research conditions, on different allowances of iodine fed as potassium iodide. The iodide administered per ewe per day in these groups being, none, 1/20, 1/5, and 4/5 grain during the major portion of the gestation period in each of three years.

Detailed records have been or are being gathered on the weights of ewes and lambs, feeds consumed and their iodine content, gestation period, wool yield, character of lambs, size of thyroids with their iodine yield, iodine percentage in the lambs' bodies, and other pertinent data. To date many of the chemical determinations are as yet incomplete, but such data as are available are discussed herein.

## HOW THE IODIDE FED EWES WERE HANDLED AND FED

The ration fed to the experimental ewes during the winter pregnancy season, in which time of the year only the potassium iodide allowances were made, was the same for all groups in any one year. In 1925-'26 the legume hay fed was soybean, but in the last two years, 1926-'28, alfalfa hay was substituted. The same amount of each feed fed the average ewe per group was kept quite constant not only in each winter season but for all years.

It is to be emphasized that the experimental conditions were controlled so as to make the iodide feeding, at different levels of intake—1/20, 1/5 and 4/5 grain per ewe daily—significant from the research standpoint. No other variants were introduced, hence the variations in the results secured, after allowing for the normal probable errors of such biological work, may be attributed to the effect of the potassium iodide allowances.

The rations fed per ewe daily were as follows:

*Lot I*—Grain Mixture A (shelled corn—natural moisture basis—60 lbs.; whole oats 30 lbs.; linseed oilmeal 10 lbs.), 1

pound divided into 2 equal feeds; 2.7 pounds of corn silage A.M. feed; 1 pound legume hay (soybean hay first year, 1925-'26, and alfalfa hay second and third years, 1926-'28), P.M. feed; and flake salt (mixed with Grain Mixture A) two times daily at rate of ½ ounce (0.03125 lb.) per ewe daily.

*Lot II*—Same as Lot I but 1/20 grain of KI fed with the salt.

*Lot III*—Same as Lot I plus 1/5 grain of KI fed with the salt.

*Lot IV*—Same as Lot I plus 4/5 grain of KI fed with the salt.

The iodide feeding was discontinued when parturition occurred, having been begun in the breeding season, at which time the ewes went into their winter dry lot quarters.

Cereal straw, practically all from oats, was used for bedding all groups; our observations were that they ate no bedding. The ewes were diverted to a small paddock on dry, sunny and otherwise propitious days, for exercise and solar irradiation.

All groups were handled alike in common yards during the suckling period, receiving Grain Mixture A, alfalfa hay, corn silage and technical sodium chloride. The KI administration was discontinued on the birthdays of the lambs. The lambs during the first 60 days after birth were fed corn grain, whole oats and linseed meal, free-choice style in a creep. The roughages and grain were discontinued when the ewes' lambs were sixty days of age, and all were then turned as one flock to blue grass pasture during the summer and early fall. The lambs were weaned at about five months. In the late fall the ewes again went into the winter quarters when they were divided into groups and again fed as hereinbefore stated. The point we emphasize is that conditions were uniform for all ewes from winter to winter season, so that the iodide allowances fed represented the variables or experimental differences.

Table V gives data on the ewes and lambs covering number of each involved together with the weights and gains of the ewes and losses in ewe weight during parturition.

## TABLE V

WEIGHT, GAINS AND LAMBING RECORD OF THE PREGNANT EWES
(Three Years of Data)

Ewes Averaged 103.7 Days in the Winter Season of Iodide Feeding
10 Breeding Ewes per Group Each Year—Averaging Approximately 184 Pounds at Start
Late November or Early December to Lambing Time the Following February and March

| Group or Lot No. and Designation | No. of Ewes Carried (3 Yrs.) | No. of Ewes Which Lambed | Average Initial Weight of the Ewes Lbs. | Average Daily Gain per Ewe Lbs. | Loss of Weight per Ewe in Parturition Lbs. | New-Born Lambs Produced per Group in the Three Years | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Rams | Ewes | Total |
| I Check— No Iodide .. | 30 | 27 | 184.6 | 0.22 | 29.2 | 23 | 25 | 48 |
| II KI, 1/20 grain | 30 | 26 | 184.1 | 0.24 | 30.3 | 22 | 25 | 47 |
| III KI, 1/5 grain. | 30 | 25 | 186.0 | 0.20 | 27.5 | 23 | 18 | 41 |
| IV KI 4/5 grain. | 30 | 28 | 181.8 | 0.24 | 27.9 | 22 | 29 | 51 |

### GESTATION PERIOD AFFECTED

The gestation period was apparently slightly lengthened through the addition of iodide to the partially iodine deficient basal ration as is evidenced in Table VI. The average period of all the check ewes, Group I, all years, was 145.83 days as contrasted with 146.16 days for Group II (1/20 gr. KI), 146.73 days for Group III (1/5 gr. KI), and 146 52 days for Group IV (4/5 gr. KI). The average of all of the iodide fed Groups, II, III and IV, shows 146.48 in comparison with 145.83 days for the check, Group I, all years, or a difference of 0.65 day. Biometrical analysis of the data indicate that if the experiments were duplicated during a three year program, under the same conditions, that the chances of Groups II, III and IV showing a longer period than the check group, I, would be respectively 77, 96 and 95 percent, i.e., 77, 96 and 95 times out of a hundred. Statistically, therefore, the longer periods of gestation encountered in our investigations to date appear to be of significance. It should be borne in mind, however, that the comparisons made by us cover the relationship existing between ewes having on the one hand a partial deficiency of iodine in their feed and water intake sufficient to cause, approximately, a doubling of the weight of the thyroid, a moderate hypertrophy; and on the other hand, ewes having an apparent sufficiency of iodine for normal reproduction.

Kalkus (1920) in comparing the gestation periods of 45

## TABLE VI

GESTATION PERIOD BY YEARS
(Averages by Groups, Annually and for Three Years)

| Group No. | I (Check) | | II (1/20 Gr. KI) | | III (1/5 Gr. KI) | | IV (4/5 Gr. KI) | | All Iodide-Fed Groups, II, III and IV, Consolidated | |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | No. Ewes Lambed | Average Gestation Period (Days) | No. Ewes Lambed | Average Gestation Period (Days) | No. Ewes Lambed | Average Gestation Period (Days) | No. Ewes Lambed | Average Gestation Period (Days) | No. Ewes Lambed | Average Gestation Period (Days) |
| 1925-26..... | 10 | 146.53 | 7 | 146.82 | 9 | 146.92 | 10 | 146.51 | 26 | 146.74 |
| 1926-27..... | 8 | 144.97 | 10 | 145.35 | 9 | 146.82 | 9* | 146.21 | 28 | 146.10 |
| 1927-28..... | 9 | 145.80 | 9 | 146.54 | 7 | 146.50 | 9 | 146.84 | 25 | 146.64 |
| Total..... | 27 | | 26 | | 25 | | 28 | | 79 | |
| Av., straight†... | | 145.77 | | 146.24 | | 146.75 | | 146.52 | | 146.50 |
| Av., weighted§.. | | 145.83 ± .20 | | 146.16 ± .22 | | 146.73 ± .28 | | 146.52 ± .20 | | 146.48 ± .12 |

*One abortion (cause unknown) not included; time, 83.41 days.
†Averaging the average periods of each year.
§Averaging all of the gestations—this being the actual average for all years.

ewes giving "normal births" with 8 ewes presenting "goitrous births" found 151 and 153 days respectively. The range in the normal ewes was 16 days and in the affected ones 14 days. Goats in his experience had longer pregnancy periods when the kids were affected with goiter, 19 normals averaging 145 with a maximum range of 32 days and 27 affected having a mean of 161 with a maximum range of 62 days, a difference of 16 days in the comparable average gestation time. Kalkus says, after much contact among horsemen in the goitrous field of the northwestern U. S. A., that "The majority of reports, however, indicate that the mares (producing goitrous colts) run overtime."

Welch (1917) of Montana may be quoted: "Many ranchers report that pregnant sows carry the pigs four to seven days longer than the average period, and a great many sows die at farrowing time." The data now available on the gestation period indicate that whereas a marked iodine deficiency, accompanied with goitrous offspring, may result in a somewhat prolonged period, a partial deficiency may promote a slightly earlier delivery.

### EFFECT OF DEVELOPMENT ON NEW-BORN LAMBS

The birth weight, vigor, condition, and wool covering of the lambs (see Table VII) from the various groups were affected but little, if any, by the iodide feeding. Statistical studies of the data warrant this interpretation.

TABLE VII

BIRTH WEIGHT, VIGOR, CONDITION (DEGREE OF FATNESS), AND WOOL COVERING OF NEW-BORN LAMBS

(Average of Three Years—1926, 1927 and 1928)

| Group No. | I (Check) | II (1/20 gr. KI) | III (1/5 gr. KI) | IV (4/5 gr. KI) |
|---|---|---|---|---|
| Lambs per pregnant ewe, average | 1.78 | 1.78 | 1.64 | 1.83 |
| Lamb weights, pounds average: | | | | |
| Rams | 9.35 | 9.30 | 9.70 | 9.11 |
| Ewes | 9.60 | 9.39 | 9.79 | 9.31 |
| All, or both sexes | 9.48 ± .20 | 9.34 ± .19 | 9.74 ± .20 | 9.23 ± .17 |
| *Vigor %, average | 82 | 78 | 76 | 82 |
| *Condition %, average | 71 | 70 | 73 | 68 |
| *Wool covering %, av. | 81 | 81 | 81 | 78 |

*Based on observations made according to a relative scale, 100% being considered as the maximum. Our judgment is that differences should exceed 6% to approach significance, inasmuch as these figures do not represent actual "measured" values, but are based on appraisals.

### THE MEASUREMENTS OF NEW-BORN LAMBS

The size of the new-born lambs, as determined by certain linear measurements, is given in Table VIII. Apparently, the iodide feeding had no effect on the body height, body length, leg length, heart or chest girth, and paunch or middle girth.

**TABLE VIII**

LAMBS—SIZE AT BIRTH
(Average of three years—1926, 1927 and 1928)

| | All Measurements in Inches | | | |
|---|---|---|---|---|
| Group No. | I (Check) | II (1/20 gr. KI) | III (1/5 gr. KI) | IV (4/5 gr. KI) |
| Withers (shoulder) height | 14.17 | 14.13 | 14.10 | 14.06 |
| Leg, fore, length | 9.56 | 9.60 | 9.63 | 9.57 |
| Shoulder top to Ischium, length | 10.75 | 11.00 | 11.03 | 10.80 |
| Heart or chest girth | 14.82 | 14.90 | 14.83 | 14.86 |
| Paunch or middle girth | 15.21 | 15.18 | 15.06 | 15.31 |

### WEIGHT OF THYROID GLANDS AFFECTED BY IODINE FEEDING

Table IX gives pertinent data in regard to the weight of new-born lambs from which thyroids were taken, their sex, weight of thyroid in grams and ratio of thyroid to new-born lamb weights, together with other figures applicable to the problem in hand. This material is given by years as well as for the three years of investigation, averages being presented for the combined yearly periods.

A careful survey of Table IX shows quite clearly that the feeding of potassium iodide to the pregnant ewes affected quite markedly the weight of the thyroid glands of their resulting new-born lambs. The following deductions may be made:

1. In all three years the addition of small amounts of potassium iodide to the pregnant ewes' ration had a rather marked effect upon the average size of the thyroid glands of the new-born lambs, the weights being reduced in all instances.

2. In only one of the three years was there a break in the downward weight tendency of the thyroids. In 1927-28, Group II is somewhat out of line with the same group in the two preceding years, the average thyroid from three selected representative lambs being smaller than the glands secured from Groups III and IV receiving, respectively, four to sixteen times as much iodide. In this particular year the ewes presumably received more iodide in their basal ration because the glands are smaller than in the two preceding years, as may readily be seen

## TABLE IX

WEIGHT OF THYROIDS OF NEW-BORN LAMBS DECREASED BY IODINE FEEDING
Three Years' Results, 1926, '27 and '28 on Thyroids Removed from Selected Representative Lambs

| Group No. | I—Check | | | II—(1/20 Gr. KI) | | | III—(1/5 Gr. KI) | | | IV—(1/5 Gr. KI) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1925–1926 | | | | | | | | | | | | |
| Lamb number | 2606 | 2370 | 2212 | 2372 | 2138 | 2477 | 1901 | 2397 | 2492 | 2496 | 2435 | 2484 |
| Lamb weight, pounds | 11.0 | 12.0 | 12.0 | 13.0 | 8.5 | 9.5 | 10.0 | 8.0 | 7.5 | 8.5 | 6.0 | 10.0 |
| Lambs in litter | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Lamb, sex | Ram | Ram | Ewe | Ram | Ewe | Ram | Ram | Ram | Ewe | Ewe | Ram | Ram |
| Thyroid weight, grams | 1.1616 | 1.5607 | 1.0893 | 0.8135 | 0.8421 | 0.8656 | 1.1023 | 0.5518 | 0.6398 | 0.6605 | 0.5985 | 0.5691 |
| Thyroids weight, grams, average | | **1.2705** | | | **0.8404** | | | **0.7646** | | | **0.6094** | |
| 1926–1927 | | | | | | | | | | | | |
| Lamb number | 2656 | 2481 | 2423 | 2138 | 2672 | 2339 | 2162 | 2663 | 2535 | 2673 | 2659 | 2257 |
| Lamb weight, pounds | 8.9 | 8.2 | 8.4 | 9.1 | 9.8 | 9.2 | 8.8 | 8.6 | 7.6 | 9.5 | 7.3 | 7.9 |
| Lambs in litter | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Lamb, sex | Ewe | Ewe | Ram | Ram | Ewe | Ewe | Ram | Ram | Ewe | Ram | Ewe | Ewe |
| Thyroids weight, grams | 1.0083 | 1.3220 | 1.0810 | 1.0882 | 1.0085 | 0.7373 | 1.0440 | 0.8960 | 0.7135 | 0.6087 | 0.4255 | 0.8750 |
| Thyroids weight, grams, average | | **1.1371** | | | **0.9447** | | | **0.8845** | | | **0.6364** | |
| 1927–1928 | | | | | | | | | | | | |
| Lamb number | 2423 | 2482 | 2599 | 2306 | 2138 | 2409 | 2271 | 2162 | 2671 | 2131 | 2261 | 2374 |
| Lamb, weight pounds | 7.3 | 9.1 | 8.8 | 9.3 | 8.0 | 7.4 | 10.0 | 8.6 | 11.0 | 8.6 | 10.2 | 7.2 |
| Lambs in litter | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 3 |
| Lamb, sex | Ewe | Ram | Ram | Ram | Ram | Ewe | Ram | Ram | Ewe | Ewe | Ram | Ram |
| Thyroids weight, grams | 0.9840 | 1.1566 | 1.0728 | 0.6830 | 0.6378 | 0.7170 | 0.8555 | 0.7520 | 0.7057 | 0.8867 | 0.6821 | 0.5675 |
| Thyroids weight, grams, average | | **1.0711** | | | **0.6793** | | | **0.7711** | | | **0.7121** | |
| Three Years, Combined | | | | | | | | | | | | |
| Lamb, weight pounds, average | | 9.52 | | | 9.31 | | | 8.90 | | | 8.36 | |
| Lambs in litter, average | | 2.00 | | | 2.22 | | | 2.00 | | | 2.11 | |
| Lambs, sex— | | | | | | | | | | | | |
| Rams % | | 55.6 | | | 55.6 | | | 66.7 | | | 55.6 | |
| Ewes % | | 44.4 | | | 44.4 | | | 33.3 | | | 44.4 | |
| Thyroids, weight grams— | | | | | | | | | | | | |
| Lowest | | 0.9840 | | | 0.6378 | | | 0.5518 | | | 0.4255 | |
| Highest | | 1.5607 | | | 1.0882 | | | 1.1023 | | | 0.8867 | |
| Average of all | | **1.1596 ± .0382** | | | **0.8214 ± .0319** | | | **0.8067 ± .0389** | | | **0.6526 ± .0314** | |
| Ratio of thyroid to lamb weight 1: | | 3724 | | | 5141 | | | 5004 | | | 5811 | |

by comparing the averages of the check lots. However, this particular variation is not of much consequence in affecting the final average results, altering them but little.

3. The average weight of the thyroids for all three years in Group I, from 9 lambs, was 1.1596 grams. This group received the basal ration without added iodide. Group II, receiving 1/20 of a grain of potassium iodide per ewe daily during the winter season, showed in the new-born lambs thyroids weighing 0.8214 gram, average. Group III, receiving 1/5 grain of potassium iodide, had thyroids weighing somewhat less, or 0.8067 gram, and Group IV, ingesting 4/5 of a grain of the superimposed iodine carrier, produced new-born lamb thyroids weighing, on the average, 0.6526 gram. The thyroids from Group IV, the heaviest iodide group, weighed 56 per cent as much as the thyroids of Group I, check.

4. The question arises as to what is a normal thyroid gland in a new-born lamb. The same question arises for other animals. We are proceeding on the assumption that the smaller the thyroid, within reasonable limits, the more normal and healthy it is, providing that the percentage of iodine contained therein is reasonably high and that the gland shows no pathological changes on microscopic examination. It may be well to emphasize likewise that the new-born lambs possessing these normal thyroids should not show adverse symptoms which may be attributable to a deranged metabolism on account of this gland. We shall see later how the size of the thyroids from the new-born lambs in our experiments correlate with the iodine content, both on the percentage basis and in actual quantity of iodine stored.

5. The thyroid glands of new-born lambs represented but a small proportion of the total weight of the lambs from which they were removed. On the ratio basis, taking the weight of the thyroid as 1, the smallest thyroid, relatively speaking, was found in Group IV in the first year of the experiments. Lamb No. 2631, weighing 10 pounds, possessed a body weighing 7970 times the thyroid contained. On the other hand, the largest proportionate thyroid was exhibited by lamb No. 2731 in Group I, receiving the basal ration without iodide addition, this lamb weighing 2814 times its thyroid. On the whole, the heaviest thyroids in proportion to body were in Group I, basal ration, these lambs weighing 3724 times their thyroids. In Group II,

receiving 1/5 of a grain per ewe daily, the new-born lambs showed a figure of 5141. The figure for Group III was 5004. And for Group IV, the heaviest iodide fed lot, the relative body weight was 5811:1. These findings are in harmony with the general trend of the data as regards thyroid weights.

6. The biometrical analysis of the data, covering the weight of the thyroids secured from the various groups, shows that the mean differences existing between Group I and II, III and IV were, respectively, 6.78, 6.48 and 10.26 times the probable error, which means that the chances are practically 100 per cent in favor of iodide feeding, as practiced in this series of experiments, decreasing the weight of the thyroids of the new-born. The difference between Groups I and IV stands out, being extraordinarily significant.

### IODINE IN THYROIDS OF NEW-BORN LAMBS

The iodine found in the thyroids of new-born lambs, expressed in parts per million on both natural and air-dry basis, the actual iodine of the thyroids expressed in milligrams, and the ratio of the iodine, present in the thyroid, to the thyroid weight, fresh basis, are given in Table X. In this table the results of two years' study covering 1926 and 1927 lambings are given. The data on the third year will not be available for some time. Determinations covering the third year results as regards the iodine content of the thyroids as well as the iodine content of the bodies of the lambs which were removed for chemical analyses and other pertinent figures, including iodine analyses of the feeds, will be published in due course.

Professor J. A. Schulz and the author are co-operating on the chemical phases of these investigations, and to him is due the credit for the careful and painstaking analytical work done on the samples covering the three years of research under discussion.

In making the iodine determinations, Professor Schulz soon found that he was confronted with a number of perplexing problems in regard to methods of procedure. After several months' study he decided to use, essentially, the method of Kelly and Husband (1924), which is a modification of the third published method of Kendall (1920), with the exception that some of the procedures recommended by Kendall, but not considered neces-

## TABLE X

IODINE FOUND IN THE THYROID GLANDS OF THE NEW-BORN LAMBS
Two Years' Results 1926-'27

| Group No. | I—Check | | | II—(1/20 Gr. KI) | | | III—(1/5 Gr. KI) | | | IV—(4/5 Gr. KI) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1925–1926** | | | | | | | | | | | | |
| Lamb number | 2485 | 2370 | 2212 | 2372 | 2138 | 2477 | 1901 | 2397 | 2492 | 2496 | 2435 | 2484 |
| Iodine in thyroids, parts per million—* | | | | | | | | | | | | |
| (a) Natural | | | | | | | | | | | | |
| Basis | 574.2 | 500.7 | 606.2 | 1094.5 | 1003.8 | 2053.2 | 1328.1 | 1061.6 | 1358.7 | 1859.7 | 854.4 | 1459.1 |
| Average | | **560.4** | | | **1383.8** | | | **1249.5** | | | **1391.1** | |
| (b) Air-dry | | | | | | | | | | | | |
| Basis | 2541.7 | 2296.3 | 2717.2 | 1652.0 | 3843.3 | 7820.9 | 5594.1 | 4627.2 | 6138.9 | 6485.0 | 3894.4 | 6669.6 |
| Average | | **2518.4** | | | **5438.7** | | | **5453.4** | | | **5683.0** | |
| Iodine in thyroids, mgs. | 0.67 | 0.78 | 0.66 | 0.89 | 0.85 | 1.78 | 1.46 | 0.59 | 0.87 | 1.23 | 0.51 | 0.83 |
| Average | | **0.70** | | | **1.17** | | | **0.97** | | | **0.68** | |
| **1926–1927** | | | | | | | | | | | | |
| Lamb number | 1098 | 1100 | 1103 | 1093 | 1095 | 1106 | 1099 | 1104 | 1107 | 1096 | 1097 | 1105 |
| Iodine in thyroids, parts per million— | | | | | | | | | | | | |
| (a) Natural | | | | | | | | | | | | |
| Basis | 805.4 | 430.0 | 626.0 | 1378.1 | 2507.0 | 2004.6 | 1529.8 | 1671.3 | 1229.2 | 2305.4 | 2239.4 | 1330.3 |
| Average | | **620.5** | | | **1953.2** | | | **1476.8** | | | **1958.4** | |
| (b) Air-dry | | | | | | | | | | | | |
| Basis | 3266.3 | 1945.5 | 2397.3 | 4589.0 | 7481.7 | 6426.2 | 6761.8 | 5602.4 | 4640.6 | 6960.9 | 5736.7 | 4819.9 |
| Average | | **2536.4** | | | **6166.6** | | | **5668.3** | | | **5839.2** | |
| Iodine in thyroids, mgs. | 0.81 | 0.57 | 0.68 | 1.50 | 2.53 | 1.48 | 1.60 | 1.50 | 0.88 | 1.40 | 0.95 | 1.16 |
| Average | | **0.69** | | | **1.84** | | | **1.33** | | | **1.17** | |
| **Two Years, Combined** | | | | | | | | | | | | |
| Iodine in thyroids, parts per million— | | | | | | | | | | | | |
| (a) Natural Basis Average | | **590.4** | | | **1673.5** | | | **1363.1** | | | **1674.7** | |
| (b) Air-dry basis average | | **2527.4** | | | **5802.7** | | | **5560.8** | | | **5761.1** | |
| Iodine in thyroids, mgs. average | | **0.70** | | | **1.51** | | | **1.15** | | | **1.01** | |
| Ratio of iodine in thyroids to thyroid weight (fresh basis), average 1: | | 1693.7 | | | 597.5 | | | 733.6 | | | 597.1 | |
| Ratio of iodine in thyroids to lamb weight, average 1: | | 6,307,359 | | | 3,071,748 | | | 3,670,934 | | | 3,469,748 | |

*To convert parts per million to percentage basis move the decimal point four places to left. Example: 560.4 p. p. m. equals 0.05604%; or 1383.8 p. p. m. equals 0.13838%.

sary by Kelly and Husband, were adopted. The method used by Schulz was carefully checked on known iodine carrying samples before putting it into execution.

Deductions for the data given in Table X are presented herewith:

1. The addition of iodide to the basal ration fed the pregnant ewes resulted in an increase in the proportion of iodine in the thyroid gland of the new-born offspring. We have expressed the iodine in parts per million in order to make the figures more quickly and easily intelligible. The new-born lambs from the basal group, I, appear to have been on the border of iodine deficiency. According to Marine (1924) the iodine content of the thyroid gland, when maintained above 0.1 per cent or 1000 p. p. m., protects against goiter. One of the lambs in Group I had only 430 p. p. m. of iodine, and the average of all was only 590.

The indications are that a near-maximum content of iodine, 1,674 p. p. m., was secured by the smallest dosage, or by 1/20 of a grain of KI daily per ewe. When the dosage was increased to 1/5 of a grain the p. p. m. of iodine was lowered to 1363. A further increase of 4/5 of a grain altered the iodine content but little, 1675 p. p. m. While the larger administration of iodide decreased the size of the thyroidal structures, this atrophic effect was apparently not due to increased iodine storage. It is possible that 1/20 of a grain per ewe daily was sufficient to supply all nutritional needs; at least it so appears.

2. The maximum storage of iodine, 1.51 milligrams per gland of the new-born, was attained when the mothers received 1/20 of a grain KI per head daily, whereas the average thyroid from the lambs of Group I, on the basal ration, carried only 0.70 mgm. of iodine, or less than half as much. Since these are averages based upon two years' results, they appear quite dependable. On the other hand, the increase of the iodide allowance to 1/5 of a grain actually brought about a decrease in the amount of iodine in the gland to 1.15 mgs. And a still further increase of the iodide fed to 4/5 of a grain induced an even greater decrease, to 1.01 mgs. In consideration of the fact that the results covering the storage of iodine in the thyroid are consistent for

the two years, it would seem that the height of iodine storage in this endocrine is reached at comparatively low levels of iodine ingestion. It may be that the thyroids are relieved, in part, of their duty or duties when iodine in excess of so-called normal requirements is given.

Can it be possible that in the presence of a moderate excess of iodine in the somatic tissues that less metabolism is required on the part of the thyroid? In the absence of sufficient iodine in the tissues (or certain tissue) may it be that a certain substance (or substances) is (or are) formed which overtax the thyroid, or cause it to become toxic in itself, and thus produce hyperplasia, followed with that more serious pathological development, exophthalmic goiter? Anyhow, it is suggestive that the thyroids may decrease in size from 100 units to less than 81 units weight (compare Groups II and IV), whereas at the same time the iodine contained decreases at an even greater rate, from 1.51 to 1.01 mgm., or from 100 units to less than 67 units weight. It may be argued, of course, that the number of observations are not sufficient to warrant much philosophizing along these lines, and this hypothesis is granted. We hope to have more to contribute on these hypothetical problems as the years unfold.

3. The ratio of the iodine in the thyroid to the weight of this endocrine was as 1:1694, in round numbers, in the average lamb of Group I. The proportion of iodine was increased, 1:598, when 1/20 of a grain of iodide was fed. The ratio was 1:734 when 1/5 grain was allowed, and 1:597 when 4/5 grain was administered. The ratio of iodine to the air-dry thyroid weight shows a similar relationship, the proportion of air-dried thyroidal material for Groups I, II, III and IV to iodine being respectively, 396, 172, 180 and 174:1.

4. Parenthetically, it is well to call attention to the fact that Ames, from the domestic animal standpoint, is in a semi-goitrous region. In our herds and flocks we have observed visible external goiter in aggravated form in five out of the fifteen years since 1913. In our breeding sheep flocks on the college farms serious trouble has been experienced with goitrous newborn lambs. Much depends upon the rations fed and general

environment, because a flock on one portion of the farm may show goiters at lambing time, whereas a contemporary flock in a different area, housed in another barn, do not. When iodide feeding as a preventive measure has been resorted to, however, goiter has never shown its head in the new-born.

5. If the thyroids are enlarged sufficiently not to function adequately, it can hardly be expected that such glands would be suitable for therapeutic use. One of the reasons why summer gathered glands are preferred by some practitioners is very likely due to the higher iodine content, as well as the more normal functioning status of such glands. It is during the pasturage season that sheep, for instance, increase their iodine stores, and hence it is during this period that the glands are reduced in size. At least one would so judge, if the evidence in this paper is sufficient to prove the basal principle upon which this deduction is based.

6. The relationship existing between the weight of thyroidal iodine and the new-born lamb, as given in the lowest horizontal column of Table X, is of interest. The non-iodide fed lambs carried 1 part of thyroidal iodine per 6,037,359 parts of lamb weight; on the other hand, the administration of 1/20 of a grain KI per pregnant ewe daily caused a higher concentration, or 1 part iodine per 3,071,738 parts lamb. By carrying the iodide dosages at a higher level, 1/5 and 4/5 grain, we lessen the iodine proportions to, respectively, 1 part of iodine per 3,670,934 and per 3,469,748 parts lamb. How will larger intakes of iodide fed the pregnant ewe affect these relationships? When we have available the iodine figures in the lambs' bodies, excluding thyroids, we shall be in a somewhat better position to discuss this question of the quantitative relationship of thyroidal iodine and lamb weight.

### EFFECT OF IODIDE FEEDING ON WOOL GROWTH

The fleece or "unscoured" wool yields are given in Table XI. The results are close, but the data suggests, possibly, a slightly favorable influence. Biometrical data covering the probable error of the differences show that the chances of iodide

feeding increasing the fleece yield over the check group, not fed iodide in addition to the basal ration, are respectively 72, 86 and 63 out of 100. The combined groups, II, III and IV, fed iodide show 79 chances out of 100 in favor of an increased yield on repetition of this series of experiments. The coefficients of variation in fleece yields for the various groups were quite similar, indicating close uniformity of fleece yields within the groups as well as among the groups. It is thought that the slight tendency to increased gross yield may be due to an augmentation of the skin secretions, weighed as "grease" in the wool fleeces.

While it is true that wool-less new-born lambs are sometimes observed in cases of iodine deficiency, yet this influence may be entirely a pre-natal one, one not affecting the wool growth on growing or mature sheep. The causal agent which initiates a process may be inessential thereafter.

TABLE XI

FLEECE YIELDS OF THE EWES

(Average of Three Years)

| Group No. | I | II | III | IV | Iodide Fed Groups II, III, IV Combined |
|---|---|---|---|---|---|
| No. of fleeces... | 30 | 30 | 30 | 30 | 90 |
| Weight, lbs. av. | 8.02 ∓ .13 | 8.17 ∓ .11 | 8.35 ∓ .17 | 8.12 ∓ .17 | 8.21 ∓ .09 |

## SUMMARY

Iodine plays an essential role in the thyroid and bodily metabolism of domestic animals. A brief survey of important literature showing the significance of iodine in domestic animal physiology and economy with its relationship to the thyroid-gland function, pathology, etc., and body development, is presented along with some philosophy, observations, and interpretations made by us.

Potassium iodide fed to swine in a semi-deficient "iodine" region, Central Iowa, resulted in greater growth (weight and dimensional) and in feed economy, even though no observable gross symptoms of any goitrous condition were noted.

The administration of iodine as potassium iodide to breeding sheep prevented goiter in the new-born lambs, but its allow-

ance in excessive dosages had apparently a deleterious influence, particularly in lessening resistance against hemorrhagic septicemia. Certain hypothetical questions covering causative factors are raised. The heavy administration of iodide to ewes caused their milk to be high in iodine for a brief period.

Increasing dosages of iodide, from none to 4/5 grain per ewe daily, decreased the size of the thyroids in the new-born lambs and increased the percentage of iodine in the glands. The milligrams of iodine per lamb thyroid was augmented by a small ingestion of iodide, 1/20 grain KI, but decreased thereafter by larger dosages, 1/5 and 4/5 grain KI. The thyroidal iodine in the lambs at birth figured on the weight basis as 1 part to 6,037,-359 (check group, no iodide); to 3,071,738 (1/20 grain KI dosage); to 3,670,934 (1/5 grain KI); to 3,469,748 parts (4/5 grain KI). Proportionately speaking, the iodine in the thyroids represent but an infinitesimal portion of the total weight of the new-born.

The correlation between the thyroid size and its iodine content, per cent and actual, of new-born lambs is altered by the quantitative allowance of KI to the ewes.

Data are presented showing the effect of the administration of iodide to sheep on growth, feed economy, gestation period, wool (fleece) growth, character of the offspring, and other items of importance.

We acknowledge with gratitude the co-operation of Professors J. A. Schulz, V. E. Nelson, C. C. Culbertson and Messrs. Hugo Nilson and W. E. Hammond of Iowa State College, the inspiration of Dr. F. M. Pottenger, Los Angeles, California, and the magnanimous courtesy of Dr. J. W. Kalkus, State College of Washington, for his most excellent illustrations showing gross symptoms of animals affected with thyroid hyperplasia and gland sections of normal and diseased animals.

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# STUDIES OF THE ENDOCRINE GLANDS

## IV. The Male and Female Gonads

ALLAN WINTER ROWE, Ph.D.
AND
CHARLES HENRY LAWRENCE, M.D.
Evans Memorial
BOSTON, MASS.

In a series of papers from this institution, a general method for the diagnosis of endocrine disorders has been described in detail (1) and the results obtained from its application to pituitary and thyroid malfunctions presented (2) (3).

This paper summarizes our results with cases showing aberrations of the primary sexual organs, the testicles and ovaries. In presenting this material, the authors earnestly desire to avoid the controversial element which has operated greatly to enlarge if not enrich the literature. To that end only the observed facts will be presented, with such conclusions as are directly warranted. Certain of our findings are distinctly unorthodox in relation to more or less generally accepted theory, and it is felt that the actual data will be more significant if unembellished with a mass of supporting polemic.

The enormous social and economic import of the exocrine functions of these glands, coupled with the usual assumption of interdependence upon the internal secretory activities, has inevitably colored thought and influenced trends of study. From earliest record, speculation has endowed the sex organs with a multitude of attributes basic to the whole scheme of existence. It remained for Brown Séquard to render concrete the surmises of Berthold—or even Bordeu, to make the happy alliteration complete—and realize an acceptable recrudescence of the best traditions of Egyptian mysticism and medieval alchemy. The influence of sex upon physical and mental habitus has long been recognized. Emasculation practised in man in conformity with various religious beliefs and in the domestic animals for economic reasons, derives from a remote antiquity. The striking outward

differences that pertain to sex in the higher forms of life and their modification by ablation of the sex glands, must early have been recognized, and as a result castration was practised to confirm certain qualities that unchecked maturation would have destroyed. Sex and reproduction are not identical, though the latter depends upon the former in the more evolved forms of life. Sex implies phylogenetic differentiation; reproduction, the fusion of the differentiated parts. It is the external manifestations which are the prime factor in reproduction which is, after all, the one essential. But conservative interpretation of experimental evidence regards a concomitant endocrine function as one essential for the proper development of those portions in which the outward capacities have their origin. Other equally potent endocrine agencies must likewise be admitted if current belief as to the genesis of pubertas praecox and kindred developmental anomalies be accepted. The more expansive—and less critical—views that merge in the function of the sex organs, the gamut of physical and mental characteristics of man, do not require discussion. The due sequence of the stadia of development leading first to maturity and later to the recessions incident to the decline of reproductive power are intrinsic, seemingly, in the proper functional adjustments, not only of the gonads themselves but of a number of other centers of endocrine activity. The genital arrests of pituitary and thyroid failure do not, a priori, connote a simultaneous loss of internal secretory function on the part of the testicle or the ovary. Ablation of the gland with the removal of those cells which are usually assumed to be the seat of endocrine activity, also robs the organism of those in which the external function is engendered. The data from incomplete supressions such as the subjects of x-ray sterilization, vasectomies and salpingectomies, and from cryptorchids, are inconclusive, since the sterilities may be no more than mechanical interferences. The degenerative changes apprehensible by careful histological examination do not exclude rigorously all traces of the parts of exocrine function. When one realizes how fractional residua are capable of maintaining function, it would seem wise to maintain a genial scepticism toward the comprehensive generalizations based on partial experiments. Transplantation studies suffer from the same objection as those involving complete ablation, since all portions of the gland

participate in the experiment. While striking results are obtained, the lower animal species seems to play the predominant part in the phenomena evoked, the sexes being unequally and not uniformly influenced in those groups where changes are demonstrable. The use of organ extracts offers perhaps the most definite potentiality, but here again the presence of extraneous active material on the one hand, or the destruction of the active principle during extraction on the other, places obstacles in the way of unqualified success. That these are in fair way to be overcome, would seem to be certain from the success that has attended the studies with others of the endocrine group. But even here a temperate conservatism must be observed. Striking as have been the results with rats and mice by the use of "follicular hormone" the alleged excitation of oestrus in the spayed female with extracts of testicles and other foreign substances raises a natural question as to the specific character of the phenomenon. A detailed recountal of the difficulties attending the solution of these several problems lies outside the scope of the present thesis.

To summarize the facts pertinent to this discussion, it may be said that the primary sex organs have respective exocrine functions from which the reproduction of the species derives. Further, there is evidence of an internal secretory function of the primary sex organs, well established in the female and probable in the male, at least in the years preceding maturity. Man, generically speaking, passes through three well defined periods of existence,* determined by the power of reproduction. In the female there is possibly a further subdivision intrinsic in the oestrous cycle and the immediate results of reproduction as manifested by pregnancy and lactation. These are, however, but incidental to her period of fertility, and merge in it in a general classification. During the first of these, the period of growth, many processes are going on in the body in which an endocrine activity of the gonads may or may not be involved. From the results of castration in this period† there would seem to be abundant evidence that such loss to the growing organism induces gross somatic changes of an unmistakable character.

*Lipschütz (4) denies this.

†The observations are based wholly on the male. The results of prepubertal castration in females is recorded only by Roberts [cited by Marshall (5)], and but little credence is attached to his reports.

Castration in adult years of both males and females is a common surgical procedure. Inversion of outward sex habitus is the common report although the somatic changes are less striking, as growth possibilities, at least of the bony structures, are definitely restricted. Castration in advanced years is attended by less striking changes though the development of marked hirsuties in aged females is, at times, referred to as a manifestation of a "physiological castration" implying suppression of ovarian function as an incident of the degenerative changes of senility.

Fundamentally, the sexes are sharply differentiated,* although many cases of apparently indeterminate sex are recorded in the literature and these must represent but a small part of existing cases. The multiplicity of genital anomalies producing this end result is not to be wondered at when embryonal relationships are considered. For example, in the series of nearly two thousand cases from which the present group are excerpted, there were three complete visceral inverts, a more comprehensive developmental aberration than hypospadias or analogous conditions which contribute so large a proportion of the pseudohermaphrodites. In dealing with the gonads then, it is necessary to treat them separately, as organically and functionally they are completely differentiated structures. Furthermore, the ovary is seemingly concerned, directly or indirectly, with a large number of important functions incident to reproduction, which find no correlative activities in the male. Finally, in the corpus luteum the ovary develops transiently a new potential source of endocrine activity seemingly independent of the other portions of the gland.

Needless to say, from any center in which a wide variety of functions find their origin, changes may occur which will influ-

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*In Neugebauer's (6) exhaustive compilation but five cases of true hermaphroditism are recorded [see Garre (7), Simon (8), Pick (9), v. Salen (10), Schickle (11), and Unger (12)] and in each of these only a single ovotestis was demonstrated, the other being unitary organ. The few other alleged cases recorded are lacking in positive demonstration. More recently, Neumann (12a) has compiled a number of cases from the more recent literature. Of the ten where ample description was available to him, he regards four at least as doubtful. An eleventh [Berblinger's (b) case] was described only in a note and cannot be passed upon. Of the six which he accepts, only one (Robert Meyer) (c) shows bilateral ovotestes. He cites an additional ten from foreign literature not to him available, of which two are doubtfully authentic, two [Briau, Lacassagne & Lagouette (d), Masson (e)] are bilateral ovotestes, and the remainder range from Burden's (f) amply provided individual with an ovary and a testicle on each side, to the more modest equipment of Baldwin's (g) patient with a left ovary and right testicle.

ence some but not all of the several activities. To illustrate, the functional level of activity of the ovary during pregnancy remains a matter of speculation. By many, an overactivity is inferred, while others see a period of quiescence with lessened functional level. Thus we may expect widely divergent pictures in the three phases of life as conditioned by reproductive activity. That the immature child should offer the same evidences as the adult is possible but not probable. Even though we concede—as is not usually done—that the reproductive mechanism is entirely independent of the normal endocrine activities of the gland, the establishment of new functions in one set of cells would seemingly influence, even though by indirection, the behavior of other cells immediately adjacent to them. The problem then is admittedly intricate, and only by limiting the variables so far as one may is it possible to arrive even at a first approximation.

The cases reported here, with but non-significant exception, are adults. Work with children in the prepubertal period calls for other standards, at present imperfectly defined, and in some cases even for other methods of approach. All of the women here reported had established the catamenia, and but two of the males were immature. The inclusion of these, as will be shown later, has larger measure of warrant than would be the case with the opposite sex. Post-menopausal cases appear among the women, as the differences in this stadium are of degree rather than of kind.

Another point requiring amplification is the designation of all of the cases as "hypofunctional." The literature contains frequent reference to a hypergonad state. We have never been privilege to see such a condition. Unquestioned hypofunction is produced by castration, and the study of a group of such cases defines a clinical and laboratory picture of fairly clear-cut outline. The antithesis of this picture we have never seen. Pubertas praecox cannot be regarded as a hypergonad state, particularly if we accept the alleged influence of other endocrine entities as causative. It becomes, under these conditions, an interesting but resultant developmental anomaly to be contrasted with the arrests engendered by pituitary and thyroid failure. A libido in excess of the usual conventional standard is certainly no warrant for the assumption of a hypergenital con-

dition. Even conventional standards vary and some allowance must always be made for the personal factor operative in normality. Further, it is well known that libido persists, sometimes for long periods, in individuals who have lost the primary sex organs in adult years. If libido be the criterion of gonad activity, we have in this fact a most uncompromising contradiction. The fact is that the assignment of restrictive limits to the normality of the sex urge is on a parity with other ex cathedra utterances unhampered by a paucity of basic fact. And above all, the fact remains that in a considerable group of individuals referred for study as hypergonad cases, not one has even suggested a clinical and laboratory picture the opposite of that produced by castration.

TABLE I
PHYSICAL MEASUREMENTS

| Observation | | Male | Female | Remarks |
|---|---|---|---|---|
| Number of Cases | | 11 | 189 | Total=200 |
| Distribution | % | 5.5 | 94.5 | |
| Age (yrs.) | High | 77 | 68 | |
| | Low | 10 | 14 | |
| | Average | 34 | 34 | |
| Height (cm.) | High | 175 | 175 | |
| | Low | 146 | 140.5 | |
| | Average | 166 | 161 | |
| Sitting Height (cm). | High | 93 | 94 | |
| | Low | 75 | 75.5 | |
| | Average | 88 | 86 | |
| Sitting Height Index | | 0.530 | 0.534 | |
| Chest (cm.) | High | 99 | 121 | |
| | Low | 79 | 60 | |
| | Average | 87 | 77 | |
| Trunk Chest Index | | 1.010 | 1.117 | |
| Weight (kgm.) | High | 80.7 | 124.0 | |
| | Low | 50.5 | 35.8 | |
| | Average | 64.4 | 60.4 | |
| Area (sq. m.) | Average | 1.72 | 1.64 | |
| Lung Volume (c.c.) | High | 4940 | 4000 | |
| | Low | 1800 | 930 | |
| | Average | 3710 | 2600 | |

Obviously, as no "hyper" state can be defined, the intermediate zone of dysfunction becomes equally impossible to designate. True, all disturbances of the endocrine glands might be termed dysfunctions, as is from time to time suggested. But with such clear-cut and sharply differentiated entities as are presented by the thyroid and pituitary for example, it bespeaks a meticulous rather than a scientific caution to insist on a carefully non-descriptive classification.

As all of our cases accord in kind, though not in degree, with the results produced by complete ablation of the sex glands, we feel warranted in designating them as hypofunctional in character.

With these introductory remarks, presented to define a position and not to excite acrimony, we may turn to the consideration of the data of the several observations. Following the sequence of the earlier papers, we may first take up the physical measurements and certain related statistics. These have been collected in Table I.

The sex disproportion is striking, and as a statistic may be misleading. Pathological changes in the testicles are seemingly of less frequent occurrence than in the ovary. Our figures probably represent a trend rather than a definition. There is a wide span of age, but as has already been noted, the prepubertal element is practically absent.

TABLE I-a

AGE DISTRIBUTION

| Years | % |
|---|---|
| 11-20 | 13.5 |
| 21-30 | 37.5 |
| 31-40 | 22 |
| 41-50 | 18 |
| 51-60 | 6 |
| 61-70 | 3 |

Only six of the women were less than eighteen, (two at fourteen and sixteen, one each at fifteen and seventeen) and, as before stated, menstruation had been established in every case in this group. This exocrine sign of maturity is conventional but is probably the best criterion to adopt. The absence of the male, castrated in prepubertal years, eliminates the abnormally tall adult eunuch, and the average height recorded compares well with usual normal standards. The women are equally not remarkable.

Sitting height indices show no departure from the normal, and the several other measurements might easily represent those of a group of healthy average individuals. The authors recognize that the elimination of the prepubertal case exercises an influence, but were they included, for proper presentation they would fall in a separate category and so be without influence

on the data as presented. The arbitrary inclusion of a group of children with the adults would synthesize an artefactual relationship that would be meaningless.

While the raw data of actual measurement have true significance, relationships of the individual to some established standard indicate a trend more strikingly. The use of the Dreyer and West standards, under limits already defined (13), offers a basis for one such comparison.

TABLE II

"VITAL CAPACITY" OBSERVATIONS

| Observation | | Male | Female |
|---|---|---|---|
| Weight | High | +34% | +107% |
| | Low | −15% | −41% |
| | +Average | +18% | +22% |
| | % | 60 | 51 |
| | −Average | −10% | −12% |
| | % | 40 | 49 |
| | Net Average | +7% | +5% |
| Chest | High | +19% | +66% |
| | Low | −2% | −19% |
| | +Average | +9% | +12% |
| | % | 60 | 47 |
| | −Average | −2% | −7% |
| | % | 40 | 53 |
| | Net Average | +4% | +2% |
| Lung Volume | High | +14% | +23% |
| | Low | −58% | −67% |
| | +Average | +9% | +6% |
| | % | 40 | 11 |
| | −Average | −17% | −22% |
| | % | 60 | 89 |
| | Net Average | −7% | −19% |

The few males vary within far more restricted limits than do the females. This may result from the paucity of observations in the male series. Certainly there is not apparent that tendency to obesity that is considered a cardinal evidence of gonad failure. Tandler and Grosz (14) recognize two types of eunuch, the "tall" and the "fat," and consider that these repeat in the eunuchoid group. In this series there is obviously not enough obesity to conform to the one, and the heights recorded in Table I eliminate the other. In other words, neither by castration nor by destruction of gland function by disease in adult years, is the typical habitus of the prepubertal castrate necessarily realized. Numerous other records show that in a percentage of cases they do conform, but the observation may

well be a result of extraneous causes. Certainly in this carefully studied group there is no defined tendency toward a typical obesity. On the other hand, the majority of the cases fell within the limits of a relative normality. The chest repeats the weight comparisons, as naturally could be predicted. The lung volume comparisons show a definite sex difference. The men are compared to Dreyer's standard "A," comprising athletes, soldiers, sailors, and active outdoor workers. The male gonad failures average but 7 per cent below this rather rigid standard, though the constituent members were not engaged in the active pursuits of Dreyer's classification. The women, on the other hand, are compared with Dreyer's female standard "B," and even under these more elastic conditions, fall, on the average, 19 per cent below prediction. Any impairment of normal vigor tends to be reflected moderately in this measurement. The striking feature is the relatively normal performance of the men.

The data from certain urine examinations are presented in Table III.

TABLE III

URINE MEASUREMENTS

| Observation | | Unit | Male | Female |
|---|---|---|---|---|
| Volume | High | c.c. | 1440 | 3000 |
| | Low | c.c. | 460 | 230 |
| | Average | c.c. | 1120 | 1130 |
| Spec. Grav. | High | | 1.032 | 1.035 |
| | Low | | 1.011 | 1.005 |
| | Average | | 1.021 | 1.019 |
| Albumin | | % | 9 | 27 |
| Casts | | % | 9 | 19 |
| Sugar | | % | 0 | 23 |
| "Urobilinogen" | | % | 0 | 0 |
| Amylase Index | Av. | | 18 | 16 |
| Salol | Av. | min. | 75 | 81 |
| Urea Curve | Normal | % | 60 | 54 |
| | Delayed | % | 0 | 24 |
| | Progressive | % | 0 | 6 |
| | Low | % | 40 | 16 |
| Phenol Sulphone Phthalein 2 hour Elim. | Av. | % | 51 | 55 |

The sex differences here in the main are slight. A possible exception is the seemingly greater incidence of renal disturbance in the female group, an expression conceivably of nutritive disturbance of the kidney. The one salient difference is the appearance of glycosuria in nearly one-fourth of the female cases,

it being totally absent from the other group. This will be discussed at length in the section devoted to carbohydrate tolerance.

In spite of the evidences of kidney disturbance, the phthalein test shows a slightly higher value for the women. The difference is scarcely significant. To summarize the data of this table, the men show a uniform normality that is somewhat striking, while the chief aberrations of the female group lie in certain evidences of a kidney disorder, which may well be referable to a disturbance of nutrition and in a frequent slight glycosuria. The nitrogen partition data given in Table IV but repeat the first indications. High risidual nitrogen has been previously shown to be associated with metabolic disturbance of endocrine and non-endocrine regulators. In the present case, the percentage of male cases exceeding the conventional limit of 9 per cent is less than in a series of non-endocrine disorders. The female group equates in frequency with the pituitary and the thyroid groups, falling short only of the adrenal, with which superimposed nephritis is almost concomitant. Further, the male average is well below, the female slightly above the limiting value that our experience has established. That hypogonadism in the female engenders certain metabolic disturbances, is the only conclusion that one may draw. The inevitable corollary is that the testicle gives no evidence in these studies of a similar influence.

TABLE IV

NITROGEN PARTITION

| Observation | Unit | Male | Female |
|---|---|---|---|
| Total Nitrogen.....Av. | Gms. | 11.34 | 8.46 |
| Urea Nitrogen.....Av. | % | 83.6 | 80.3 |
| Uric Acid Nitrogen.....Av. | % | 1.9 | 2.1 |
| Ammonia Nitrogen.....Av. | % | 2.8 | 4.0 |
| Creatinin Nitrogen.....Av. | % | 4.3 | 4.5 |
| Residual Nitrogen.....Av. | % | 7.4 | 9.1 |
| % = or > 9.0%..... | % | 36 | 48 |

The blood chemistry naturally equates with the urine findings, being the source from which the latter originates. Certain of the results are grouped in Table V.

At first sight it would seem as if the blood findings of the male presented an opposite picture from those of the urine. All the nitrogenous constituents are higher, and in the case of the

TABLE V

BLOOD CHEMISTRY (AND SEROLOGY)

| Observation | Unit | Male(1) | Female | |
|---|---|---|---|---|
| Non-Protein Nitrogen.....Average | mgm. | **36** | **31** | |
| % > 35 mgm..... | % | 36 | 14 | |
| Urea Nitrogen.....Average | mgm. | **16** | **14** | |
| % > 17 mgm..... | % | 27 | 16 | |
| Uric Acid.....Average | mgm. | **3.6** | **3.2** | |
| Net (2) % > 4.0 mgm..... | % | 11 | 8 | Total Average =8% |
| Creatinin.....Average | mgm. | **1.7** | **1.5** | |
| Residual Nitrogen.....Average | mgm. | **18.1** | **15.3** | |
| Sugar.....Average | mgm. | **95** | **96** | |
| % > 120 mgm..... | % | 0 | 3 | |
| % < 80 mgm..... | % | 0 | 6 | |
| + Wassermann..... | % | 0 | 2 | |
| + Kahn (presumptive)..... | number | 0 | 0(3) | |
| + Spinal Fluid..... | number | 0 | 0 | |
| + Schwartz-McNeil..... | number | 0 | 0 | |

(1) While the figures for blood nitrogen are influenced by the inclusion of the two nephritics, the upward tendency is still manifest if their data are omitted.
(2) All demonstrated cases of gout and nephritis have been deleted.
(3) Test not applied to two patients with positive wassermann.

non-protein nitrogen, exceed slightly the usual normal limit. The inclusion of two nephritics plays some part, but there is an upward tendency even when their data are omitted. It may be remembered that the average nitrogen elimination of the male group was one-third greater than that for the female moiety. This too would exercise some influence but not enough to account for the disparity recorded. The really significant datum is the residual nitrogen fraction, and here a definite increase is unquestionably manifest. Omitting the nephritics, it still falls slightly above the conventional limits ($15 \pm 2$ mgm.) of the normal. In this observation we find the first real evidence of a metabolic disturbance dependent upon deranged testicular function. Blood sugar levels exhibit no sex difference, and the averages are not only rigorously normal, but the composing members almost equally so. All of the males showed entirely normal blood sugar levels which, coupled with the complete absence of glycosuria in the cases of this group, would imply an absence of testicular influence on the carbohydrate metabolism. The few females showing values above 120 mgm. reached only a maximum observed level of 125 mgm. That an emotional response may have conditioned some of the higher figures, is highly probable. Similarly, in the group falling below 80 mgm., the inferior limit was at 75, and the average for the group, 77 mgm., a decrease of very modest proportions. The significant point in this connection is the association of a strictly normal blood sugar with the observation earlier recorded of glycosuria in nearly one-

fourth of the female cases. This will be touched upon in the later discussion on carbohydrate metabolism. Before leaving these data, attention is called to the normal level of the blood uric acid throughout the series, a point of significance in the differential diagnosis of endocrine disorders, as has been shown previously. It will be noted that two positive Wassermans (1 per cent) are reported in the series. Both of these subjects were surgical castrates, and the luetic element could be regarded only as a non-endocrine disease superimposed on an established hypogonadism. On this ground, their inclusion was felt to be warrantable. Incidentally, the findings in one case agreed exactly with those of the uncomplicated castrates, and in the other, only the sugar tolerance departed from the usual finding.

The blood morphology of the two groups offers certain points of interest.

TABLE VI

BLOOD MORPHOLOGY

| Observation | Unit | Male | Female |
|---|---|---|---|
| Haemoglobin .....Av. | % | 90 | 88 |
| Erythrocytes .....Av. | $10^6$ | 5.12 | 4.84 |
| Color Index..... | | 0.88 | 0.91 |
| Leucocytes .....Ave. | $10^3$ | 8.0 | 7.6 |
| P. M. N. Neutrophiles.....Av. | % | 58 | 57 |
| % = or > 75%..... | % | 9 | 4 |
| Lymphocytes .....Av. | % | 35 | 35 |
| % = or > 33%..... | % | 55 | 56 |
| Eosinophiles .....Av. | % | 2 | 2 |
| Net (1) % = or > 3%..... | % | 27 | 21 |
| Monocytes .....Av. | % | 5 | 6 |

(1) Cases have been deleted in which a non-endocrine cause of eosinophilia has been demonstrated.

The general examination reflects the normal sex differences, the absolute values being substantially normal throughout. The differential count shows, on the one hand, no sex difference, and on the other, that slight upward tendency to the lymphocyte fraction which has already been noted in connection both with other endocrine malfunctions and also a group of non-endocrine disorders. Borchardt (15) and Sauer (16) have also both commented on a general incidence of lymphocytosis in all endocrine disorders. Antonelli (17) observed that castration in dogs lowered haemoglobin, both red and white cells and was

coupled with lymphocytosis; the latter observation was confirmed by Hermann (18) after ovariectomy. Naegeli (19) regards the characteristic picture of chlorosis as dependent on ovarian failure. He was, however, unable to determine a chlorosis in a ten-year observation of a young woman castrated at seventeen to correct a "moral insanity." The ovaries were normal and the patient had matured before the operation, however. Guggenheim (20) reports lymphocytosis in eunuchoids, and Falta (21) recognizes a constant increase of monocytes. A tendency toward a slight eosinophilia is evident, although the average value falls within normal limits. Generally speaking, the blood picture presents nothing remarkable.

The respiratory metabolism, with its concomitant measurements, has claimed a somewhat larger measure of attention.

TABLE VII

RESPIRATORY METABOLISM

| Observation | | Unit | Male | Female |
|---|---|---|---|---|
| Basal Metabolism— | | | | |
| Deviation | High | % | −1 | +9(1) |
| | Low | % | −20 | −25 |
| | + Average | % | − | +4(1) |
| | % | % | 0 | 7(1) |
| | − Average | % | −11 | −13 |
| | % | % | 100 | 93 |
| % above +10% | | % | 0 | 0 |
| % between +10% and −9% | | % | 36 | 36 |
| % = or below −10% | | % | 64 | 64 |
| Blood Pressure | Systolic Average | mm. | 109 | 111(1) |
| | % < 110 mm | % | 73 | 62 |
| | Diastolic Average | mm. | 65 | 69(1) |
| | % < 65 mm | % | 73 | 15 |
| Pulse Rate | Average | per min. | 67 | 75(1) |
| % = or < 70 | | % | 73 | 31 |
| Respiration Rate | Average | per min. | 15 | 18 |
| % = or < 10 | | % | 9 | 9 |
| Temperature | | deg. F. | 98.0 | 98.1 |
| Alveolar $CO_2$ | Average | mm. | 41 | 35 |
| % > 35 mm | | % | 91 | 60 |
| % = or < 30 mm | | % | 0 | 26 |

(1) The positive basal rates in this group are somewhat questionable, as the nervous element cannot be wholly eliminated. Certain other observations are likewise influenced by this factor. The determinations were made with the utmost care and the data may be regarded as representative for this type of case.

Only the effects of castration need be considered in detail. The ignorance of functional level during pregnancy, indicated by the contrary opinions that have been offered, eliminates this state from present consideration.* The influence of menstrua-

*One of us (22) has shown in an extended study that the average basal rate shows a progressive increase during this condition, exceeding that determined by increased body weight (from —8 to +8 per cent during the last thirty-six weeks). Sandiford's (23) explanation that this increase represents the foetal surface contribution, invokes uncertain extrapolation, and is based on the study of a single case.

tion is likewise not pertinent, as it interjects one more element of variation which is not yet clearly related to the internal secretory activities of the gland. The general, but by no means universal, impression seems to be that there is a slight increase during the period. From another standpoint, there is no ground, a priori, for the assumption that the menopause should condition any change. The cessation of the exocrine function of the gland certainly does not prove a like inhibition of internal secretion. The applicability of the Harris-Benedict (24) equation for women, and the Aub-duBois (25) generalization, have been verified by us with a number of normal women well past the menopause.* Turning to the results of castration, Zuntz's (26) reports can at once be discarded, since his patients were not in a basal state. Curatulo and Tarulli (27), Loewy and Richter (28), Murlin and Bailey (29), Kojima (30), Angolitti (31), Heymans (32), Korenchevskii (33), and Tsubura (34), all report animal experiments in which castration produced a lowering of the basal rate in moderate degree. Lüthje (35) observed no change but his animals were not basal. Bertschi (36) with Asher could find no difference in castrated animals of either sex. Gräfe (37) in 1923 concludes that only exceptionally will ablation or loss of function produce a lowering of the basal rate, an opinion in which duBois (38) seemingly concurs. Plaut and Timm (39) report a temporary lowering, but as their "castration" is produced by x-ray sterilization, the observations hardly equate with the foregoing records, nor do they seem to warrant the rather comprehensive generalizations which the authors offer. Critical analysis of their results would lead to conclusions quite other than those presented. To summarize, it may be said that existing evidence is contradictory and opinion divided.

The data of our own series would seem to demonstrate a slight but unmistakable depression of the respiratory metabolism. In the group of castrated women without other demonstrable complication, the values range from —7 per cent to —23 per cent, the average of the group being —14 per cent, or substantially that of the entire series. The data of the com-

*Twenty women ranging from fifty to seventy-seven, with an agerage of sixty years, showed basal rates from —1 to +12 per cent, with an average of +5. A similar group of 29, the ages of whom lay between 50 and 78, with an average of 57, exhibited rates ranging from —1 to —12, the average in this case being —5. Unpublished data.—A. W. R.

plementary male group show an average of only —8 per cent, less than that of the complete male series. The limited number of the male cases, however, precludes a generalization which is warranted in the female series. A further point which bears directly on the observed magnitudes is implied in the foot note of the table. It has been our experience that the women presenting gonad failure exhibit, in a peculiar and marked degree, a quality of nervous tension and irritability (v. i.). Basal tests with them are far less satisfactory than with any other type of endocrine failure. An inability to remain absolutely quiet for even the period of a basal rate determination is frequently remarked, and this destroys the absolute basality of the measurements. While all observed basal rates determined by open or closed circuit methods are to be regarded as maxima*, in our opinion, the nervous instability of the female hypogonad is more likely to assume detrimental magnitudes than in any other condition studied. It must be remembered further that this source of error operates uniformly irrespective of the method used. Benedict and Benedict (40) have called attention to the serious error which may result from even minor muscular activity, and our own experience amply confirms their conclusion. The same disturbing element is operative in blood pressure and pulse rate measurements. These effects are too well known to require comment. Loss of function of the gonads would seem to depress blood pressure in both sexes, and possibly the pulse rate in the male. Averages are conceivably misleading, as has already been pointed out, and the relatively large number of female hypogonads exhibiting hypotension of a significant degree, is concealed in this necessary form of presentation. As a matter of fact, 62 per cent of the female series showed systolic blood pressures below 110 mm., and many of these were below 100. The definite lowering of the male blood pressure is seemingly a tangible evidence of an existing influence. Respiration rates and body temperatures show no departure from the normal in either sex.

In the last datum of the table, the alveolar carbon dioxide, a definite sex difference is found. Tensions in the male are entirely normal; in the female, on the other hand, there is a marked

*In such measurements all of the potential sources of error—barring only the gross mistake of spent soda lime or faulty gas analysis—operate to increase apparent oxygen consumption.

downward tendency which, in one-fourth of the series, produces levels ordinarily associated with acidosis. A like depression of $CO_2$ tensions in pregnancy was first recorded by Hasselbalch (41) and his findings were confirmed in detail by one of us (42). A possible import to this observation will be discussed later.

The last observation of the series here recorded deals with the carbohydrate tolerance. Prior to the establishment by one of us (43) of an intrinsic sex difference in the metabolism of galactose, but one record of a similar study was recorded in the literature. Artom (44) found that spayed bitches possessed an unchanged tolerance for invert sugar.* More recently, Tsubura (34) using glucose, has observed that castration of rabbits of both sexes lowered sugar tolerance. Estes and Burge (47), using paramecia, have demonstrated an increased sugar consumption by the organism under the stimulus of ovarian hormone. Burge and Williams (48) had previously noted a similar effect with insulin. In presenting the data here assembled, a word of explanation is necessary. As the entire matter has been discussed at length elsewhere (49), only brief explanatory notice is offered here. While the galactose tolerance of the male is totally uninfluenced by age or level of reproductive activity, the female tolerance is seemingly directly dependent upon the maturity and condition of the ovaries. Briefly, the prepubertal child gives a positive test with 20 grams; with the onset of the catamenia she advances to 30, and ultimately (usually within the year) to 40 grams, the normal level of the adult matured woman. With the menopause the tolerance level may remain at 40 or sink to 30 grams.† With a changing tolerance, the individual records of the tolerance dose in grams are insusceptible to collective reporting. By expressing changes in tolerance as percentage variations from the norm of the given individual, data are produced which possess a parity in their indications. Although the male tolerance is a constant, the same method of expression is adopted for the sake of uniformity. The data are given in Table VIII.

*De Fellippi (45), quoting Quarta, recorded a result similar to the writer's with dogs, using glucose as the test sugar. Allen (46) denied the validity of these findings.

†It is not to be understood that abrupt transitions take place. The figures given are conditioned by the method of applying the test, which has been fully described elsewhere (50).

TABLE VIII

GALACTOSE TOLERANCE (1)

| Observation | | Unit | Male | Female |
|---|---|---|---|---|
| Tolerance Dose | High | Grams | 30 | 30 |
| | Low | Grams | 30 | 20 |
| % above normal | | % | 0 | 0 |
| % equal normal | | % | 100 | 0 |
| % below normal | | % | 0 | 100 |
| Average Deviation from normal | | % | ±0 | —44 |

1. The following cases are omitted from the tabulation as superimposed non-endocrine disturbances mask the gonad influence:
   a. Two male castrates with tolerance at 40 gms. (+33%) had demonstrated late chronic interstitial nephritis.
   b. Three aged females showing normal post-menopausal tolerance (30 gms.) had demonstrated severe chronic interstitial nephritis.
   c. Four females, with tolerance averaging —80% below normal, were suffering severally from lesion of central nervous system (2), syphilis (1), and liver disorder (1). These conditions exercise a definite depressing influence on sugar tolerance.

The differences here exhibited are of the utmost diagnostic importance. Castration in the male is without influence on the galactose tolerance. Seemingly the testicle is not concerned with the regulation of the galactose metabolism. The effect on other sugars is at present unknown and is to be investigated. The omission of two male cases not recorded in the table is explained in the foot note.

Incidentally, the lessened permeability of the kidney, arising in an established nephritis, is a factor that should be considered in all forms of tolerance testing depending on urine findings. Unimpaired permeability should be demonstrated by test, and if there be indication of lowered kidney function, due allowance must be made in the interpretation of results.

Reverting to the table, we find that in every case lowered activity of the ovaries determine a lowered galactose tolerance. Further, in the castrates and severe functional failures, the level is at 20 grams. With the incipient or less severe functional cases the depression is less i. e. to 30 grams. It must be remembered that this series includes only females in whom the menstrual function has been established. What the effect would be of castration in prepubertal years is now a matter of conjecture, but from the data here and a number of unpublished observations, it seems probable that the prepubertal level of twenty grams would remain unaffected.

The striking point, from the standpoint of differential diagnosis, lies in fact, that while failure of the posterior lobe of the pituitary raises tolerance to a marked degree, and thyroid failure exercises either no influence or produces a slight increase, loss of function of the ovaries determines a decrease in tolerance to apparently a low limit of 20 grams. [The four cases which we have studied showing lower tolerances are already covered by the foot note (3) of the table.] The failure of the testicle to affect the galactose metabolism has only a less diagnostic significance, and indirectly bears upon other germane problems to be discussed later in this paper.

Before taking up the next portion of this paper, a word of explanation is necessary.

It will be noted in the foregoing discussion that but meager reference is made to the work of others. There is, of course, a most extensive literature bearing upon the subject in general, and ranging from the admirably careful, painstaking studies involving a wealth of experimental data, to those treatises designed to exploit some method of rejuvenation based upon manipulation of the organs of generation. Unfortunately for comparative purposes, a vast amount of this work deals with animal experiments that are inapplicable to the thesis in hand. A further hampering condition lies in the concentration on changing secondary sex characteristics as criteria of modified internal secretory activities. As these are certainly influenced by other agencies, at least in man (see discussion above), such observations, while striking and of the utmost import, bear but little relation to the work in hand. For example, so admirable a compilation as that of Lipschütz (4), collating a vast amount of original research with an equally exhaustive and selective canvass of the literature, contains no reference to the influence of the gonads on many important phases of metabolism. Again the emphasis laid upon the reproductive powers, which are certainly not solely intrinsic in internal secretory activity, obscures the issue.

Such pertinent observations as we have found in the literature have been incorporated in the running comment on the data reported by us. The meager tale of citations attests solely to the relatively slight consideration that has been given to this field of study.

PART II

Turning next to the clinical aspects of the condition, in reviewing the literature one is impressed with the lack of clear-cut definition of the hypogonad syndrome. It is true that a vast bibliography exists dealing with the influence on menstruation and on fertility. But there is missing, so far as the authors can ascertain, those graphic pictures so frequently presented in descriptions of many of the other endocrinopathies. There are, however, a few definite symptoms upon which observers are agreed, and these together with the more frequently considered features of the reproductive function will be considered in the light of our own findings. For obvious reasons, the two sexes will be discussed separately. The ovarian group has been augmented by a few later cases, and unless otherwise specified, the later statistics will derive from this larger series. The composition is given in the next table. Interesting members of the several groups will be discussed in detail later.

TABLE IX

OVARIAN GROUP

| | |
|---|---|
| Primary Ovarian Failure | 200 |
| Castrates (premenopausal) (1) | 21 |
| Castrates (postmenopausal) | 2 |
| X-Ray Sterilization | 1 |
| Female Pseudo-Hermaphrodites | 2 |
| Practical Amenorrhoeics (2) | 2 |
| TOTAL | 228 |

(1) Operated upon at an average age of 38 years.

(2) One of these, matured at 17, nearly 3 years later had had but 3 periods; the other matured at 14 and had had 4 periods in 11 years.

Practically all of the patients in the group were American born. No racial incidence was traceable in the very imperfect records available. The family history can best be presented in tabular form. The records are confined to immediate relatives. A number of the patients reported "nervousness" as a common familial trait. The term is an elastic one, and as applied to an immediate family may only reflect the patient's own nervous

TABLE X

FAMILY HISTORY

| *Disease* | Per Cent | |
|---|---|---|
| Cancer | 20 | |
| Diabetes | 8 | 13 |
| Other Endocrine | 5 | |
| Tuberculosis | 23 | |
| Insanity | 11 | |

instability. The mental attitude of the patient with ovarian failure is touched on below.

A review of the chief complaints as offered by the patients themselves is most informative. In some cases, more than one disability was recorded as of basic importance, which explains the numerical discrepancy. Small groups without primary significance have been omitted.

TABLE XI

CHIEF COMPLAINTS (PATIENTS')

| | |
|---|---|
| Fatigue | 72 |
| Headache (1) | 35 |
| Mental and Nervous Disorders (2) | 55 |
| Convulsions | 7 |
| Gastro-Intestinal Disorders | 20 |
| Pain (1) | 23 |
| Menstrual Disorders (3) | 28 |
| Sterility (4) | 6 |
| Obesity | 21 |
| Vertigo | 8 |
| Deafness | 20 |

(1) Not primarily associated with menstruation.

(2) Fourteen Psychoses with 5 attempted suicides, 11 Psychoneuroses, 30 Neuroses.

(3) See Table XV.

(4) See Table XVI.

Fatigue and weakness, cardinal symptoms in the other endocrinopathies, here characterize one-third of the entire group and as a secondary feature, they appear in the majority of the remaining cases. Headache is another important part of the clinical picture. Its dominance has already been noted in the pituitary and thyroid groups also. The number of established

psychoses is interesting. A causal relationship here is still to be demonstrated; the observation, however, is possibly suggestive in the light of known mental deviations associated with physiological modifications of ovarian activity. Irritability and depression are frequently mentioned as features of a failing ovarian function. Record as to the first must depend almost exclusively on outside information, as the egocentric "hypogonad" usually lacks a philosophic objectivity in personal prospective. The authors have previously noted, however, the definite warrant for the inclusion of this sign as a most characteristic finding. Many of the patients name the second as a feature of their general condition.

In this connection a few words may not be inopposite on personality changes associated with depressed ovarian function. Comment has already been made of a similar condition in thyroid disease although the formula of its expression differs from that produced by ovarian failure.

An insistantly expressed egoism is the keynote of the hypogonad character. Coupled with, and dependent on, this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies. Hyper-emotionalism and self-pity are united with an attitude of acid criticism of environmental conditions that are always unsatisfactory. The psychological study of the average woman suffering from ovarian insufficiency would be a profitable though scarcely a pleasant task.

The cases presenting convulsions were practically all established cases of epilepsy. Again, a causal relationship remains to be established. Gastro-intestinal disorders are among the well recognized sequelae of ovarian failure. In this group, four patients had demonstrated gall bladder disease, and but very few failed in their histories to give some evidence of disorder of the alimentary tract. Constipation was an usual finding, 54 per cent recording it as a chronic state. Only five patients complained of diarrhoea.

Pain, as such, was offered by 10 per cent of the patients as a primary cause of disability. Localization was rarely specific, although the lower half of the trunk was usually included in the picture. In a few cases, at least, a very definite subjective element was demonstrable.

The cases presenting menstrual disorders and sterility will be touched upon later. Twenty-one patients offered obesity as a principal difficulty. As a matter of fact, 71 of the group were over 15 per cent above prediction and in many instances, far in excess of this modest level. On the other hand, an equal number were more than 10 per cent below their calculated weights (Dreyer) while the remaining 38 per cent fell within these reasonable limits. From these figures it is clear that ovarian failure certainly does not always determine obesity. Tandler and Grosz (14) have described a "tall" type but the emaciated group does not conform to this designation. In this connection, it seems to the writers possibly significant that with the pituitary there is the non-obese Lorain Levi type of failure; they have themselves described an underweight hypothyroid type; while in the ovarian group, as many are significantly under as are overweight. The underlying metabolic disturbances deriving from endocrine malfunction would seem to manifest themselves uniformly in a variety of ways.

In 8 of the cases, vertigo was a primary complaint, while a large number of the remainder gave it as one incident in the general disease picture. Hot flashes were by no means so common as might be inferred from the usual records in the literature. The majority, but not all, of the postmenopausal patients, both of natural and surgical origin, reported this symptoms, but it was conspicuously absent from the histories of a large part of the younger women. This would suggest, perhaps, that it is significant only in the more severe established cases and a sign of a marked hypofunctional level.

The age of onset and the duration of the chief complaint is potentially interesting. With many of the presenting symptoms, the onset was undoubtedly gradual and their first recognition coincident with some event which was, in many instances at least, unrelated to the underlying disorder.

The relatively large percentage reporting an onset during the years of adolescence and early childbearing is a possible point of interest though too great weight should not be placed upon it in view of the uncertain character of the data from which it derives. A second feature in the table is the upward progress of the duration until the menopausal age, at which

TABLE XII

ONSET AND DURATION OF CHIEF COMPLAINT
(200 Consecutive Cases)

| *Interval* | *Age of Onset* | *Average Duration* |
|---|---|---|
| From birth | 6.0% | 26 years |
| 0-10 years | 3.3% | |
| 11-20 years | 32.0% | 3 years |
| 21-30 years | 31.3% | 6 years |
| 31-40 years | 16.0% | 9 years |
| 41-50 years | 6.7% | 13 years |
| 51-60 years | 2.7% | 11 years |
| 61-70 years | 2.0% | 12 years |

time it apparently becomes stationary. This too may be an artefactual relationship; it is recorded only as a statistic.

The incidence of the more common infections as derived from the history has been reduced to tabular form. The relative frequencies would seem to indicate a definite degree of susceptibility to the commoner complaints.

TABLE XIII

INCIDENCE OF EARLIER INFECTION

| *Disease* | *Per Cent* |
|---|---|
| Measles | 86 |
| Whooping Cough | 61 |
| Mumps | 50 |
| Chicken-pox | 49 |
| Influenza | 30 |
| Scarlet Fever | 22 |
| Pneumonia | 12 |
| Diphtheria | 11 |
| Rheumatic Fever | 10 |
| Typhoid | 9 |

Yet another datum is found in the record of previous surgical manipulation of the pelvic organs. As already noted (Table IX), there were 23 castrates in the series of 228 consecutive cases. In addition to these were the following: (See Table XIV.)

In other words, including the castrates, one woman in every four had had at least one laparotomy (several reported as many as four or five) for surgical manipulation of the pelvic organs,

and 7 per cent more had been curetted for reasons unassociated with any of the incidents of pregnancy. Several of such matters will be discussed at length in a later paper.

TABLE XIV

| | |
|---|---|
| Laparotomy for | |
| Unilateral oöphorectomy | 14 |
| Resection of ovarian cysts | 5 |
| Resection of uterine fibroids | 2 |
| Uterine abscess | 2 |
| Uterine suspension | 12 |
| Therapeutic curettage (excluding miscarriage) | 16 |

The importance of a thorough physical examination has been stressed throughout these papers. A few of the more significant observations may next be recorded.

The prevalence of skin eruptions is one usual finding that our records do not entirely confirm. Acne was common, it is true, but this mild inflammatory condition is associated with too many other disease states for it to assume any specific meaning here. But three of the entire group recorded skin eruptions as major complaints, two with eczema and one with psoriasis. Vulval pruritis is usually considered to be a frequent manifestation and this is scarcely to be wondered at, in the light of the frequent incidence of glycosuria. Two of our cases presented this condition as a complaint and a number of others recorded earlier attacks.

In view of the frequent allocation of hypertrichosis to adrenal disease, our own figures are of more than passing interest. Unfortunately, no record of pilosity was made in some of the earlier cases. In 134, however, in which complete observations are reported, 62 or 46 per cent showed marked hypertrichosis and of these, 45 had a definite male configuration of the pubic hair. As already noted, Falta's cited cases of adrenal disease with virilism all showed a concommitant ovarian involvement whenever record was made. The authors do not feel that their own observations settle the question; they record only a number of cases presenting excessive pilosity with retrogression of certain secondary sex characteristics, in which no evidence of an adrenal complicity was demonstrable. True, the pluriglandular

enthusiast might adduce this observation to support his thesis, but the hypernephromata associated with virilism are commonly interpreted to indicate adrenal overfunction, a condition that would ill accord with many of the laboratory findings in this series. Further, if pubertas praecox derive in many cases from adrenal overfunction, one faces again an antithetical and contradictory series of facts which cannot be explained away.

Nearly 10 per cent of the cases presented deafness as a chief complaint. As one of the author's associates has shown [Drury (51)] endocrine failure may be a factor in otosclerosis, and a number of these patients were referred for study on that basis. A fraction of them proved to be true otosclerotics, but the remainder demonstrated defects of infectious origin, establishing a purely non-endocrine etiology for the deafness.

That the calcium metabolism is influenced by the level of ovarian function is generally conceded although the mechanism must be regarded as wholly unknown.

One-third of the entire series showed evidence of past or present gravely defective teeth, while an additional 12 per cent were reported with the teeth in "fair condition" only. The cross section of the social background of the group precludes neglect as the primary causal agent.

Diseased tonsils have already been noted as of very frequent occurrence in pituitary and thyroid disease. The present group offers no exception to the previous record. Forty-four per cent of these patients had had one or more tonsillectomies, while the laryngological examination showed an additional 24 per cent with definite tonsillar infection. The total of 68 per cent compares favorably with the incidence of all of the commoner infections with the exception of measles. Whether a disturbed metabolism of endocrine origin predisposes to a lowered resistance to infection or focal infections influence selectively the level of endocrine function, is a question for the future to settle. The high coincidence in the conditions discussed would seem to indicate a possible inter-relationship.

A number of the patients (15 per cent) showed some thyroid enlargement, in fact several of these were referred as probable thyroid cases. In no case was the enlargement marked and equally, in none of them was thyroid disease demonstrable.

Residence in so-called goiter districts, the sequelae of child bearing and similar agencies, were apparently responsible for the occurrence of these non-toxic goiters.

The routine heart examination developed reportable abnormality in 20 per cent but grave cardiac conditions were rare. As previously noted, 10 per cent of the group had had rheumatic fever. Similarly, while 16 per cent gave evidence of past or present pulmonary disease, a number of patients with a history of asthma or hay-fever and a few cases of healed tuberculosis accounted for practically all of them. In no case was there any apparent relationship between any chest condition and the presenting endocrine disease.

A general tenderness on deep palpation of the abdomen was reported by 11 per cent of the group. In view of the surgical histories recorded, added to the subjective attitude of many of the patients, the number is small. The gall bladder cases all showed tenderness in that area, but with the others, the definition was usually vague.

Diminished or exaggerated reflexes were exhibited by one in three, but beyond these and one doubtful Babinski, the routine neurological examinations were not remarkable.

Turning now to a consideration of the exocrine functions (in the regulation of which, in the last analysis, endocrine activities may be implicit), the age of the establishment of the catamenia invites attention. The accompanying graph (Graph I) gives the records of 197 cases in this series. One child maturing at 7 and the two pseudo-hermaphrodites are not included. Seventy-five percent fall within the conventional 12 to 14 year limits, while over half (28) of the remainder impinge upon the chronological limits of the restricted group. Ten per cent only, show a definitely retarded maturity; two of the patients are in the group later castrated, a rigorously just proportion. If the figures obtained are meaningful, ovarian failure would seem to be either an incident of the years of maturity or, if a prepubertal existence be assumed, without signal influence on the fact of maturation. One child had a unilateral oöphorectomy at 12 and menstruated at 13. The others were operated upon much later and after maturing. The subsequent menstrual histories are presented in tabular form.

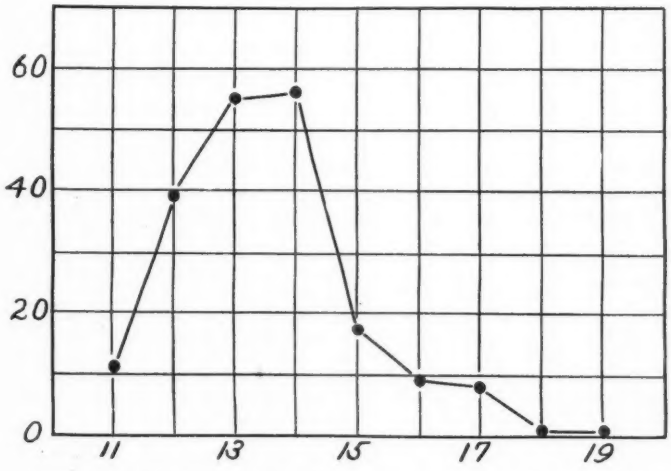
TABLE XV

MENSTRUATION (214 CASES)

| Period | —Amount of Flow— Diminished | Normal | Increased |
|---|---|---|---|
| Irregular (39%) | | | |
| Increased | 14 | 36 | 13 |
| Decreased | 3 | 5 | 9 |
| Both | 1 | 0 | 3 |
| Total | 18 | 41 | 25 |
| Regular (61%) | 23 | 83 | 24 |
| Total | 41 | 124 | 49 |
| | 19% | 58% | 23% |

Regularity and amount of flow are the two variable elements considered. In view of the frequent statement that ovarian failure presupposes a disturbed menstrual function, these figures are enlightening. Nearly two-thirds of the group record a normal rythmic incidence of the function, and a slightly smaller number present a normal flow. Eighty-three (39 per cent) are both regular in rythm and normal in amount. Another usual statement that ovarian failure shortens the interval is far from substantiated by these records. Of the irregular

PLATE I




Maturity curve. Number maturing at each year. Omits one child menstruating at seven years, and two female pseudohermaphrodites who never menstruated.

group, only 17 show an accelerated recurrence, while nearly four times that number have delayed periods. If one considers the absolute incidence of shortened interspace in the entire series, the percentage shrinks to wholly unconvincing proportions. Four patients, only, show that double irregularity which is so common a feature of thyroid failure. Avoiding dogmatism, it may be said that in this series, ovarian failure has a tendency to lengthen the menstrual interspace in that smaller proportion which depart from the conventional rythm.

One very striking fact may be commented on in passing. In Table X, only 28 of the patients offered menstrual disorder as a chief complaint, although 84 report irregularity of the function and 24 an increased flow. Even more significant is the fact that 136 of the group reported dysmenorrhoea of varying degrees of severity. The disproportion between the actual incidence and its presentation as a disability emphasizes the pathetic acceptance of painful menstruation by the average woman as a normal complement of the exercise of this particular physiological function.

It will be remembered that six of the patients offered sterility as the cause of presentation for study. The fertility data are interesting in this connection. It should be stated that, of the augmented group, 121 were unmarried (53 per cent) and the remainder had had one or more matrimonial experiences. The relative equality of the two groups may bear on the elimination of sexual inactivity as a predisposing cause to gonad failure. In the writer's opinion, the series is too restricted to indicate more than a possible trend. The fertility data are given in Table XVI.

TABLE XVI

FECUNDITY (100 CASES)

| Group | I | II | III | IV |
|---|---|---|---|---|
| Miscarriages | 0 | A = 2 | 0 | Av. = 2(1) |
| Children | 0 | 0 | Av. = 2 | Av. = 3 |
| Number | 31 | 10 | 34 | 25 |
| Duration of Marriage— | | | | |
| Longest | 32 years | 21 years | 30 years | 28 years |
| Shortest | 1 year | 2 years | 3 years | 2 years |
| Number < 5 years | 13 | 4 | 2 | 1 |
| Total Average | 8+ years | 11+ years | 13+ years | 18 years |

(1) Omitting 1 case with 24 miscarriages. See text.

Four permutations are possible as exemplified in the four groups. In all the cases recorded, contraception was specifically denied. When this has been practised the degree of fecundity in the non-pregnant naturally remains a matter of conjecture. For obvious reasons induced abortions are likewise omitted.

Nearly one-third have never been pregnant, while 10 per cent more have conceived but have been unable to complete their pregnancies. While lues cannot be ruled out absolutely in any case, all of the patients presented here, with but two exceptions, had negative Wassermans and, in many cases, negative Kahn tests as well. The two exceptions fall in Group IV, having borne children as well as having had miscarriages.

Forty-one per cent of these patients were sterile at the time of study and, even if these subjects be deducted who had been married less than five years, the remainder (24 per cent) falls notably above the average percentage of infertility as recorded by others. Reynolds and Macomber (52) conclude that from 10 to 12 per cent represents a fair measure of infertility and in this estimate they are unable to eliminate those arising from contraception. On this basis the present figures show an augmented degree of infertility of striking proportions. One-third of the group have completed all of their pregnancies successfully and one-fourth have conceived several times with average result of 60 per cent productivity. As noted above, one case is omitted from the computation of the miscarriages since, after bearing one child, she subsequently had 24 incomplete pregnancies, the husband being luetic. The point of note in this case is the very high initial fertility of the couple which, in spite of all handicaps, permitted 25 impregnations. The patient's weary tale was ended by a panhysterectomy several years before entering the clinic. At no time did she give any evidence of specific disease and at the time of her study the serological tests were uniformly negative.

As was stated in the first paper of this series and reiterated in the later discussions, the various special examinations serve the primary purpose of determining the presence or absence of a non-endocrine disorder to which the patients disabilities may be referred. Only exceptionally, and this is peculiarly true of the present group, do they add positve evidence of an endocrine

involvement. A brief partial analysis of 100 selected cases in which a total of 574 special examinations* were performed, may be considered.

*Eye:* Of a total of 90 examinations, 72 gave positive findings. Enlarged blind spots were found in 46, while patients with disc defects such as tallow color, indistinct margins, etc., were 24 in number. Twenty-two showed contracted fields, of which 6 demonstrated a symmetrical contraction of marked degree. Stiff pupils were found in four cases, and two showed the so-called "snuff fundi" usually regarded as a sign of congenital syphilis. Two scotomata were delineated and one case a recognized atrophy of unknown cause.

*Ear:* Of 20 ear examinations, 7 showed infective processes and the remainder defined otosclerosis. One-third of 18 Barany tests gave positive evidence of labyrinthine disease. Fourteen of 22 audiograms showed marked loss of aural acuity and the remainder indicated only a lesser degree of impairment.

*Neuro-psychiatric:* Examinations were made of 63 of the series. The results can be presented in tabular form.

TABLE XVII

NEURO-PSYCHIATRIC DIAGNOSES

| | |
|---|---|
| Psychoses | 9 |
| Psychoneuroses | 6 |
| Neurasthenia | 11 |
| Hysteria | 2 |
| Epilepsy | 6 |
| Organic disease | 7 |
| Chorea | 2 |

The seeming discrepancy between these figures and certain of those recorded in Table XI is due to the fact that a number of the patients were referred from institutions where the nervous and mental elements had already been evaluated.

*Radiography:* Ten patients showed small, shallow or otherwise remarkable sellae. None of them gave evidence of pituitary tumor. The impossibility of delimiting the normality of the sella

*The average for the entire series is slightly less than three per person. In many instances "Short Form" subjects fail, for a variety of reasons, to return for all of the special tests requested. Averages in later series, however, are much higher, i. e., "Long Form" 8+, "Short Form" 5+.

shape has already been noted (53). Sinus involvement was found in 14 of the cases studied. A past or present pulmonary disease was demonstrated in 13 patients; six of these showed a protein sensitivity. Seven gave x-ray evidence of cardiac enlargement, confirming the number demonstrated by the electrocardiograph. Eight out of 13 gastro-intestinal series showed disease, chiefly in the appendix, while one Graham test (intravenous) was positive in five performed.

*Pelvic:* Of the 55 cases examined, 13 gave evidence of some disorder, chiefly in the uterus. One infantile and one juvenile organ were found; the others were chiefly fibroid tumors.

Of the numerous other examinations, none gave data of sufficient interest to warrant comment. It will be noted from the above that none of the findings were especially pertinent to the positive determination of endocrine disease. Even the eye results, although they indicate a large degree of metabolic disturbance, fall short on any specific endocrine indication, in this group.

Limited as are the clinical indications, outside of the functions intrinsic in reproduction, which are regarded as characteristic of ovarian failure, the complementary testicular picture is even more circumscribed in detail. The study in adult years of males castrated in childhood offers some help, it is true, in defining characteristics of what may be designated as early eunuchoids. But without more objective methods of analysis than have been applied to this problem, there is always the unresolved question with the latter group if the observed genital arrest is more than one secondary evidence of early pituitary or thyroid disease—resultant and not causal. Studies of adult castrates whose glandular ablation has occurred after maturity has been established are extremely rare in the literature. Falta (21) comments on this and, in spite of the wealth of clinical material at his command, is constrained to present as his illustrative case an individual who contracted gonorrhoea with bilateral orchitis and, later, lues before tuberculosis necessitated a bilateral orchidectomy which lessened but did not obliterate his libido et potentia coeundi at the age of 26. In his 37th year he had a goiter which later spontaneously receded, and Falta saw him seemingly when 49 years of age. Falta comments on the disturbing elements, but states that the patient recorded his

modified habitus as first appearing after the operation.

The overgrowth of the long bones due to retarded epiphyseal closure, the lowered sitting height index arising from this cause, and a gradual assumption of an outward female habitus with modified pelvic contour are primarily referable to failure in youth. Even so, Tandler and Grosz (14) recognized both a fat and a tall type, although they state that the latter manifest a tendency toward characteristic fat desposition.

The four eunuchoid cases in this group show respectively sitting height indices of 0.514, 0.520, 0.525 and 0.550—in other words, one only, the 10-year-old child exhibits a significantly low value, while another is markedly above the normal average.

A loss of body hair with a feminization of the pubic contour is not confined to malfunction of the testicles, as numerous pituitary studies have shown. A wrinkled skin and some pigmentation are other features recorded, but in the main, there is a notable dearth of informative and suggestive detail. That this should be the case is in no small measure implicit in our findings. As has been emphasized repeatedly in these papers, male castration in adult years produces but minor changes in functional levels as ascertained by objective methods. In the main, the physical picture of the adult castrate presents a definite and general normality. The present small group is composed of men castrated in adult years (3), of cases of bilateral orchitis as a sequel to mumps in the years following puberty (4), and boys and young men exhibiting a marked arrest of sex development (4) in whom no evidence of pituitary or thyroid disease could be demonstrated by careful and detailed study.

With so small a group and one so divergent in the several elements that compose it, a statistical analysis is meaningless. A few comparisons may be drawn with certain of the more significant findings in the ovarian group. Five of the eleven gave fatigability as their chief complaint, and the majority of the remainder reported it as an important secondary symptom. Four were referred for genital underdevelopment, and two for sterility. Of the eight adults but three were married, and all were sterile save the aged man whose orchidectomies had been performed in the preceeding two years. One of the castrates subsequently married and was able to have intercourse with his wife

to her satisfaction (see case B-42 in next section). Diseased tonsils were again prominent, five having had them removed, while four others showed infection. Three of the four eunuchoids (10, 13 and 16 years) were of an obese feminine physical habitus, the remaining patient being spare but with somewhat broad pelvis. Body hair was usually scanty although this feature, as one might anticipate, was less marked in the castrates and post-orchitics. Constipation was an almost uniform finding, even more markedly than in the female group. The other findings lack a sufficient degree of concordance to be significant.

In the next section, typical case protocols from each of these groups will be given and will serve to elaborate the thesis presented above.

## PART III

## Case Protocols

To complete the paper, the authors desire to present a few of the cases in detail. In reviewing them, the reader is reminded that many of the factors contributing to the diagnosis could not be included here. Emphasis will be laid upon those points which may be correlated with the matters which have been discussed in the earlier pages.

### GROUP I. GENITAL ANOMALIES.

**Case B-21. Pseudohermaphrodite.** The patient's chief complaint was of obesity from which she stated she had suffered since early childhood. The history which we obtained was very limited and as events transpired not entirely ingenuous. During the course of the study several anomalies in the laboratory picture developed, and as a result one of us questioned the patient much more searchingly in regard to her history. She then acknowledged that she had never menstruated and was what was called an "hermaphrodite." She had been cognizant of this condition since early childhood but her family, for religious reasons, had refused to allow any physical examination and in the few years that had elapsed since their death the earlier inhibition had persisted.

*Family History:* Was entirely devoid of significant information.

*Past History:* The patient reported minor ailments and, later, the information given above.

*Physical Examination:* The patient was markedly obese, the hair soft and abundant, the thyroid not enlarged; the breasts were mod-

erate in size and essentially feminine in contour. There was reported a slight cardiac murmur at the apex which was later denied. There was abundant pubic hair with a tendency to male configuration, marked pilosity on the legs and a slight mustache. Routine neurological findings were normal.

*Laboratory Summary:* The patient was 33 per cent overweight; a basal rate of —11 per cent was recorded, and this was probably somewhat above the truth; blood pressure was low. Alveolar $CO_2$ was a low normal. The residual nitrogen fraction of the urine showed an upward tendency. Galactose tolerance was half the normal for a woman of the patient's age. The urea curve was normal. The blood morphology showed a substantially normal picture.

*Radiographic* findings of the skull and sella were normal.

*Pelvic examination* disclosed a congenital absence of the vagina and a prominent clitoris 1½ cm. in diameter.

*Discussion:* The general picture presented was that of ovarian failure. Because of the patient's obesity and the other impediments it was impossible to demonstrate the ovaries. One interesting fact

TABLE XVIII

| | Genital Anomalies | | | | Homosexual | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | 4 | 5 |
| Case Number | B-21 | B-946 | B-812 | B-1008 | B-408 | B-530 |
| Sex | F | F | M | M | F | F |
| Age (yrs.) | 34 | 4.5 | 4.5 | 5.0 | 36 | 19 |
| Height (cm.) | 166 | 120.5 | 129.5 | 137.4 | 164 | 169 |
| Weight (kgm.) | 83.5 | 23.2 | 28.8 | 33.2 | 43.6 | 79.2 |
| Weight Deviation (%) | +33 | −19 | −19 | −22 | −29 | +23 |
| Lung Volume Deviation (%) | — | −2 | −48 | +3 | −27 | −4 |
| Basal Rate Deviation (%) | −11 | 875 cal.? | 1058 cal.? | 1260 cal.? | −13 | +5 |
| Blood Pressure (mm.) | 110/78 | 96/50 | 96/58 | 104/56 | 102/62 | 110/62 |
| Pulse Rate (per min.) | 66 | 88 | 70 | 86 | 76 | 71 |
| Temperature (deg. F.) | 98.0 | 98.0 | 98.2 | 98.8 | 97.9 | 99.0 |
| Alveolar $CO_2$ (mm.) | 39 | 43 | 42 | 38 | 31 | 38 |
| Urine Volume (cc.) | 1440 | 380 | 530 | 1120 | 440 | 1420 |
| Spec. Grav. | 1.015 | 1.028 | 1.024 | 1.015 | 1.029 | 1.020 |
| Albumin | 0 | + | 0 | + | 0 | 0 |
| Casts | 0 | 0 | 0 | + | 0 | 0 |
| Sugar | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Nitrogen (gms.) | 10.73 | 5.37 | 6.35 | 8.11 | 5.42 | 11.74 |
| Residual Nitrogen (%) | 8.4 | 10.9 | 16.0 | 10.7 | 5.8 | 5.4 |
| Phen. Sulph. Phthal. (%) | 72 | 63 | 65 | 60 | 64 | 49 |
| Galac. Tol.— | | | | | | |
| Normal (gms.) | 40 | 20 | 30 | 30 | 40 | 40 |
| Observed (gms.) | 20 | 20 | 10 | 20 | 20 | 20 |
| Deviation (%) | −50 | +0 | −67 | −33 | −50 | −50 |
| Blood— | | | | | | |
| Non-Protein Nitrogen (mgm.) | 27 | 32 | 32 | 30 | 32 | 32 |
| Uric Acid (mgm.) | 3.5 | 3.8 | 3.2 | 3.5 | 2.2 | 3.3 |
| Sugar (mgm.) | 98 | 100 | 75 | 83 | 87 | 86 |
| Haemoglobin (%) | 100 | 85 | 98 | 95 | 90 | 90 |
| Erythrocytes ($10^6$) | 5.76 | 4.11 | 6.63 | 5.32 | 4.39 | 4.51 |
| Leucocytes ($10^3$) | 10.40 | 8.55 | 8.50 | 12.45 | 8.00 | 5.70 |
| Neutrophiles (%) | 68 | 47 | 55 | 56 | 32 | 55 |
| Lymphocytes (%) | 29 | 44 | 31 | 30 | 63 | 38 |
| Eosinophiles (%) | 2 | 3 | 0 | 2 | 1 | 2 |
| Monocytes (%) | 1 | 6 | 14 | 12 | 4 | 5 |
| Misc. (%) | 0 | 0 | 0 | 0 | 0 | 0 |

1. Pseudo-hermaphrodite (female).
2. Pseudo-hermaphrodite and Pubertas Præcox (female).
3. Pubertas Præcox (male).
4. Homosexual (male).
5. Homosexual (female).

*Observed heat production (see below).

given by the patient was that for many years she had had a headache which would last about one day, and which came at four-week intervals. During the day of the headache she had frequently noted that her perspiration had a peculiar and somewhat offensive odor. From the fact that the secondary sex characteristics had developed, it seems fair to assume that the patient presented a genital inadequacy, and that some ovarian tissue was present. Another point worthy of note was that her sitting height index was practically normal, the long legs of the so-called eunuchoid being absent. A surgical opinion was requested and it was decided that there would be no real advantage to the patient through surgical interference.

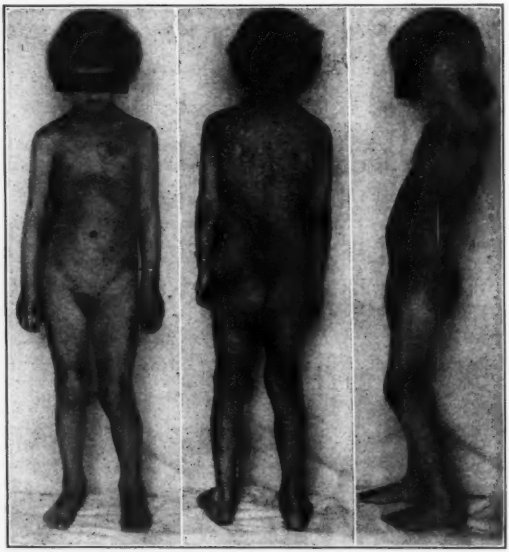
CASE B-946. PSEUDOHERMAPHRODITE WITH PUBERTAS PRAECOX. This little patient was a child four years and seven months of age who was first seen in the Out-Patient Department. The family physician had referred her for an investigation of a definite genital anomaly. The child had a hypertrophied clitoris resembling the penis of a boy of 12. In addition there was a definite growth of pubic hair although the breasts were still rudimentary. Outside of the genital condition the child was in perfect health. The study was undertaken to resolve the sex of the patient and equally to ascertain the cause of the precocious puberty.

*Family History:* The father, mother, and one older sister are living and well and present no anomalies. A second child, a male, born before the patient, cut his first tooth at eleven months, talked at twelve months, walked at sixteen months, and weighed 40 lbs. at the time of his death from meningitis shortly before his second birthday. The patient's genital anomaly was recognized when she was but a few days old. The family physician, however, most judiciously advised delay in attempting any modification.

*Past History:* The patient weighed 10 lbs. at birth, cut her first tooth at eight months, talked at twelve months, and walked at eighteen months. She had pertussis at 2½, discharging ears for about a fortnight at eighteen months, but had otherwise been a strong, active, healthy child.

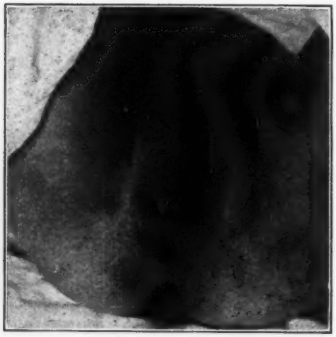
*Physical Examination:* The patient was a well developed, somewhat undernourished child between four and five with abundant hair on the head; a suggestion of slight exophthalmos was noted, but other observation demonstrated that this was a familial characteristic. Her ten upper and ten lower teeth were in fair condition. The tonsils were large and cryptic. The voice was somewhat deep and the speech slightly thick. A single pea-sized gland was felt in the upper right anterior cervical chain. It was not tender. The breasts were undeveloped and the nipples suggested the male type. The heart, lungs, and abdomen were normal. There was a considerable amount of brown pubic hair extended from the upper border of the symphysis, separating on either side of the hypertrophied clitoris. This latter was 4 cm. long, 1.3 cm. in diameter, and suggested a penis and glans after circumcision. There was no evidence of any orifice. The whole structure curved downward over an opening immediately beneath it about 1 cm. in diameter. At the upper edge of the apparent vaginal orifice could be seen the urethral opening. The vaginal slit was overhung by folds of hair-covered skin resembling labia majora. There was no evidence of scrotum, testicles, or patent inguinal canals. During the examination the clitoris became erectile. There was no axillary hair or other abnormal pilosity. The patient's gait on walking was noted to be a little clumsy.

PLATE II



Case B-946

PLATE III



Case B-946

*Laboratory Summary:* The child was distinctly tall for her age, 19 per cent under her predicted weight, and with normal lung volume. The basal rate was determined by a series of observations as 875 calories. Comparison with the age standard, which would be obviously unfair, gave her a value of +17 per cent. With the area, height and weight standards of Benedict-Talbot (54), the observed and predicted practically coincided. By the Harris-Benedict (24) standards and the Bailey (55) area computation, she was about 20 per cent below prediction. It may be safely said that the child did not present a high basal rate and it was our feeling that the rate was probably slightly though scarcely significantly low. The blood pressure was low, the pulse slightly rapid. $CO_2$ was normal. The several urines showed a very scanty volume with good elimination in relation to the patient's weight. Albumin was constantly observed. The average protein intake was somewhat low, the residual nitrogen fraction high. She reacted positively with 20 grams of galactose, negatively with 10. This would be normal value for a female child in the prepubertal period and a depressed tolerance for a boy of the same age. The blood uric acid was relatively high. The blood was lymphoid in type, showed a 3 per cent eosinophilia, and a slight secondary anaemia.

*Audiogram:* Showed substantially normal hearing.

*Ear Examination:* The ear drums were markedly thickened.

*Barany:* Normal reactions were obtained.

*Nose and Throat Examination:* The tonsils were enlarged but not demonstrably offending.

*Chest Examination:* The findings were normal.

*Neurological Examination:* The examiner regarded the patient's gait as normal and found no evidence of organic nerve lesion.

*Pelvic Examination* confirmed the statement given above, and noted that the labia were rather rudimentary and defined the existence of a vagina. No internal genitalia could be palpated, which would be explained by the patient's youth.

*Radiography:* The skull showed a persistence of the frontal suture and convolution impressions on the inner table. The sella and sinuses were normal. The chest was normal.

*Cardiogram:* Normal findings were obtained.

*Eye Examination:* The patient was too young to permit delineation of the visual fields. The fundi showed snuff pigmentation throughout.

*Urea Index:* A normal value of 155 was obtained.

*Lumbar Puncture:* This was felt necessary in view of the eye report. The pressure was 18 cm., rose to 26 cm. on pressure, returned to 18 cm. with removal of pressure. When 15 cc. of fluid was removed the pressure fell to 12 cm.

*Spinal Fluid* was strictly normal.

*Discussion:* At this point there were two definite problems to be considered. First, the sex of the child, in order that the interpretation of the various laboratory data might be as exact as possible. There was, further, the important social problem which could become acute in the course of a few years. The second question was the basis of the patient's precocity. Three endocrine factors come certainly

into question, with possibly a fourth. Over-activity of the gonad, pituitary overproduction, and tumor of the adrenal cortex have all been recorded as causative agents. While the case for the first is less well sustained and would probably imply tumor growth, it can not be ignored. The fourth possibility is, of course, the pineal, but here the evidence is even more doubtful. If the child had a cortical tumor, surgical intervention was essential, and as they are usually malignant the time factor had to be reckoned with. Further, exploratory laparotomy would aid in the resolution of the child's sex as well as make possible removal of an adrenal tumor if one were found. On this basis permission for laparotomy was requested from the parents and was granted. The child was operated upon by Dr. T. E. Chandler, to whom we express our sincere thanks. We quote directly from Dr. Chandler's report:

*May 10, 1928:* "This operation was made for the purpose of determining the sex of the child, and also with the idea of locating, if possible, the cause of her condition. Incision was made in the median line of the abdomen. Exploration was first made of the kidneys and no departure from the normal was found in either kidney. The pelvic parts were then examined. In the median line, extending upward from what seemed to be a normal sized cervix, was a cord about ½ cm. in diameter and enlarging to 1 cm. in diameter, about 2.5 cm. in length. It was flattened anteroposteriorly and was not more than ½ cm. in thickness. This was evidently a rudimentary fundus uteri. Springing from the cornua are normal tubes such as would be found in a girl of about her size with ovaries normal for her apparent age. Exploration was made of the canal of Nuck; no evidence of testicles was found here or in the labia. The wound was closed with layer sutures of catgut and stay sutures of silk worm gut.

*"May 19, 1928:* The sex of the child having been determined as that of a girl, with the consent of the parents an enlarged clitoris was removed. A circular incision was made about its base which was dissected up from attachments and the wound closed with sutures of catgut."

The determination of the child's sex as female eliminated one uncertainty in the interpretation of the data. At the present time we feel that hypergonadism and, equally, cortical tumor can be eliminated from the picture. The remaining condition, pituitary involvement, is not clearly defined although offering some supporting evidence. The more remote possibility, a pineal involvement, is also to be held in consideration. On the basis of probability the child has pituitary involvement. She will be studied at frequent intervals in the hope of resolving the matter within a reasonable period of time. Through the courtesy of the mother we were able to make a rather complete study of her. Elaborate analysis is omitted in the interest of economy of space. The general picture was one of normality, exhibiting solely an essential hypertension. Pelvic findings were devoid of features germane to the present matter. The serological findings, as well as the remaining picture, were normal.

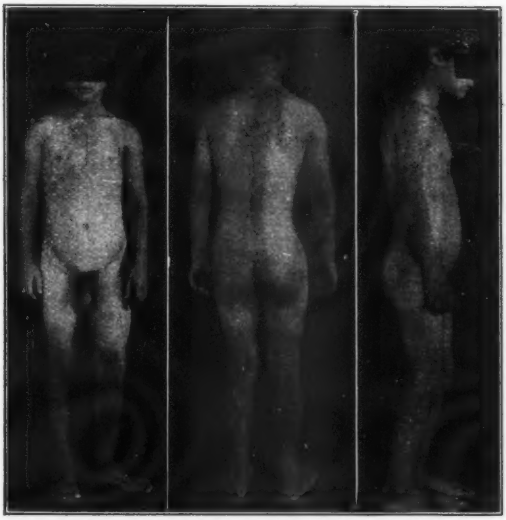
CASE B-812 AND B-1008. PUBERTAS PRAECOX. The case of this patient is reported as in some ways it parallels that of the preceding patient, although no doubt as to the sex existed. The patient was a 4½-year-old boy with stature of a lad of nine, strong, muscular and vigorous, with large genitalia, well-grown pubic hair and other evidences of maturity. As his early puberty was of possible endocrine origin, he was submitted for the study to ascertain if possible its cause.

*Family History:* The patient is the second child of five, born in an interval of six years, to parents who were, respectively, 21 and 19 at the time of the patient's birth. At the time of the patient's admission the mother, at the age of 22, was far along in her sixth pregnancy. The other children and the father and mother are en-

tirely normal and nothing which bore on the case could be elicited concerning the grandparents.

*Past History:* While the mother was on her way to the hospital to be confined she met with an accident, but sustained no serious injury. The delivery was normal but delayed. The boy's first tooth appeared in the seventh month, he walked in the fifteenth, and talked at two years of age. He had whooping cough and chicken-pox. The history was otherwise not relevant. His large size and unusual genital development were first noticed at the age of one. As he has grown he developed a number of behavior problems which led to his reference to the Fernald School. Through the courtesy of Dr. Ransom Greene, to whom we express our sincere thanks, his records have

PLATE IV



Case B-812

been made available. His school comment on social history is: "Egotistical, quarrelsome, selfish, stubborn, seclusive, somewhat resentful of authority, a leader, difficult to control. Shows no affection for mother. Teases other children." His moral reactions: "Steals and hides things. Masturbates. Started fire in a tin pan. Developing delinquent tendencies." At the time of his first contact with the Fernald School his intelligence quotient was 93.

*Physical Examination:* The boy had the appearance of a well-developed and nourished lad of nine, of strong, sturdy build, the knee and ankle joints being especially large. The voice was of deep, male type, the genitalia of adult size and development with some pubic hair. Fine, light hair covered the face, neck and arms; that of the

head was thick, light and fine. There was a small amount of discharge in the nasal cavities. Twenty first teeth were present, those in front being widely spaced; several large cavities were noted. The tonsils were large, the thyroid was not palpable. The pulse rate was somewhat rapid, and there was a slight systolic murmur at the apex. Examination of the abdomen was somewhat unsatisfactory. The penis was 9 cm. long in a relaxed state; scrotum and testicles were of proportionate size. There was a slight tendency to spasticity in the legs, most noticeable in the adductor muscles, producing a peculiar type of gait. At times the patient experienced difficulty in voluntary separation of the legs. The routine neurological examination gave substantially normal findings.

*Laboratory Summary:* The boy was, by normal calculations, 19 per cent underweight, which is actually not the case, as his sitting height index was very high (.57); his lung capacity was about half that of prediction. The standards for the basal rate at this

PLATE V

Case B-812

age are not well defined. His observed rate in the best of a series of observations was 1058 calories. An independent measurement by Dr. Fritz B. Talbot, to whom the authors express their indebtedness, gave a value of 1145. Neither of these rates was probably quite basal. Comparison with the various standards show a range of from +39 per cent by the age standard to —22 per cent by Bailey's area standard. The several Talbot values are slightly higher than the lowest observed rate. The age value is patently meaningless and we felt in this case as in the one just discussed that the rate was either normal or slightly depressed. The blood pressure was low, urine volume low, protein intake slightly low, residual nitrogen fraction definitely high. The sugar tolerance was much depressed, the blood sugar slightly below the conventional normal. The blood morphology showed a slightly high red count and an increase in the endothelial leucocytes. A long series of blood pressure measurements showed an average of 96 systolic and 55 diastolic.

*Radiography:* The frontals and sphenoids were undeveloped; the sella was small with thick posterior clinoids. Hands, wrists and knees show the development of a 12-year-old boy. The mediastinal shadow was slightly enlarged. A gastro-intestinal series was entirely normal. At one of the earlier examinations it was thought that a mass could be demonstrated in the neighborhood of the right kidney. This was not confirmed by later examinations, but it was felt that the matter should be thoroughly investigated and a pyelogram of the right kidney was taken which gave entirely negative results.

*Cystoscopy* gave normal findings.

*Bilateral Ureteral Catheterization:* Normal function was demonstrated in both kidneys.

*Chest Examination* gave normal findings.

*Orthopedic Examination:* The examiner found evidence of beading at the costochondral sutures, suggesting an earlier possible rachitic condition.

*Nose and Throat Examination:* The tonsils were found to be hypertrophied and infected.

*Neurological Examination* gave normal findings.

*Abdominal* findings were normal.

*Eye Examination:* Owing to the patient's age the fields could not be demonstrated. Enlarged blind spots were detected by use of the Lloyd slate. Remaining findings were normal.

*Urea Index:* Value of 72, which implies a loss of permeability,

*Discussion:* This case, like the one previously discussed, gave evidence of a precocious puberty, the primary cause of which could not be completely ascertained by the study as given. The patient's low blood sugar, which was confirmed by several observations, and the consistently low blood pressure were suggestive of lowered adrenal function in which presumably the medulla would be primarily involved. On the other hand, the various genitourinary examinations argued against a cortical tumor of any magnitude. The lowered sugar tolerance, as has been shown by one of us, would be entirely consistent with an adrenal insufficiency. The mediastinal shadow could be interpreted in several ways, among which could be a persistent thymus. With the very dubious case for an endocrine activity of this gland it was felt unnecessary to consider this possibility as of primary significance. If there were an adrenal tumor its prompt removal was essential. On this basis permission for an exploratory laparotomy was received from the parents. The patient was operated upon by Dr. R. C. Wiggin, to whom the authors express their indebtedness. We quote:

> "Under ether, operation was performed by making incision in the right semilunaris opening into the abdominal cavity. The intestines were pulled to one side and both kidneys palpated. There was no evidence whatsoever of tumor in either kidney, but I incised the posterior peritoneum and freed the kidney and examined the adrenal region on both sides. No disease was found. The peritoneum was then closed and a large appendix was removed by the cuff method. The wound was closed with catgut and silk worm gut."

With the adrenals probably eliminated, no evidence of testicular involvement, and the pineal and thymus of a very dubious endocrine activity, the pituitary remains as the most probable of the endocrine agencies concerned. The case was far from clear cut, however, as there were missing a number of findings of pituitary disease. That

the youth of the patient might be a factor in this was obvious but, lacking standards, interpretation became a matter of opinion. The little patient presented a considerable social problem. With a mentality on a parity with his age, a physique of a boy of nine, and adult sexual development, it was evident that the child would have to be safeguarded. Through the courtesy of Dr. Greene, and with the consent of the parents, the child was committed to the Fernald School with the understanding that he would be studied at six-month intervals in the hope that the trend would establish a diagnosis. The second study has just been completed (see B-1008). He has grown 8 cm. and increased 4.4 kgm. in weight. His weight is still 22 per cent below prediction, but the comment on the inaccuracy of the earlier standard still operates, the sitting height index being unchanged. His observed basal rate has increased disproportionately so that he is 64 per cent above his age prediction and but 13 below that of the area formula of Bailey. He is 6 per cent above the Harris-Benedict prediction. On this basis it seems to us possible that the interpretation of the earlier measurements was in error and that the predicted basal really lower than the higher value to which we gave the greater weight. This matter will be resolved as time goes on. The blood pressure has increased a little, the pulse is more rapid, $CO_2$ is diminished—this probably due to some incooperation on the part of the patient. The urine volume is now normal, but the urine shows both a very slight trace of albumin and a few hyaline casts. The protein intake is better, the residual nitrogen much lower, though still above the normal. The sugar tolerance has increased but is still below the normal. Blood sugar is now in the normal range and the leucocytic formula is substantially as before, the actual number of the white cells, however, defining a slight leucocytosis.

*Radiography:* The hands, wrists and knees present the same picture as before, the sella is slightly larger with the thick posterior clinoids still present. The mediastinal shadow is somewhat smaller.

*Neurological* findings normal, as before.

*Nose and Throat Examination* shows the tonsils enlarged but less evidence of infection.

*Cardiogram* is normal.

*Eye Examination:* The eye grounds are still unobtainable. The discs are now reported as yellowish.

The present picture is somewhat more suggestive of a pituitary disturbance but again falls short of any real definition. The boy's behavior has improved and he showed a much larger measure of cooperation than at the time of the first study. During his first stay in the hospital he stole some matches and set his bed on fire. During his second stay, under the same degree of supervision, there were no overt acts. He had been reported to us as a bed-wetter but in neither of his hospital stays has this been in evidence.

The boy will be examined at intervals of six months. At the present time we feel warranted in reporting him only as unclassified, though there is some suggestion here of a possible pituitary involvement. Neither this case nor the one preceding is to be regarded as showing deviation of the endocrine function of the gonads. In fact, they certainly derive from other endocrine causes than the sex glands. Presenting, as they do, however, evidences of an early maturity which has frequently been classified as due to "hypergonadism," it has seemed worth while to discuss them for the negative value which they possess.

GROUP II. HOMOSEXUAL

CASE B-408. The patient gave as her chief complaint general fatigability, general lack of endurance and interest, and mental depression. The condition apparently dated back to puberty. At the age of 17 there was a nervous breakdown, and at the age of 32 a second and more severe attack, requiring committment to a sanitarium. After eight months' stay here the patient attempted suicide with a revolver. The bullet passed through the skull, inflicting seemingly no permanent serious injury. The patient developed homosexual tendencies which first found expression at about the age of puberty. There had been at least four distinct attachments, one of which was in progress at the time of her hospital admission. The patient assumed the passive role. After her suicidal attempt she convalesced in some measure from the mental condition and ultimately returned home. Her fatigability, however, increased, and for the last few months she has been incapacitated for any sort of physical exertion.

*Family History:* All the members of the family were somewhat highly strung. There was no history of disease conditions of significance.

*Past History:* The patient reported minor ailments, scarlet fever, a severe abscess on the left thigh, tonsillectomy at the age of 21, and other events noted above. She complained of frequent headaches, not relieved by glasses. The appetite was poor, bowels were regular. She established the catamenia at 15½; the flow was regular but distinctly scanty. She had always been much underweight. She disclaimed all interest in the male sex, acknowledged her homosexual tendencies, but stated that they were under complete control. This, like several other statements, was misleading.

*Physical Examination:* The patient was a slightly built, thin and undernourished woman in her mid-thirties. The hips were narrow and the general body configuration that of an adolescent boy. The head showed the scars of two bullet wounds, but was otherwise not remarkable. Teeth were in fair condition. There was a somewhat asymmetrical chest expansion; the breasts were small and undeveloped. Pubic hair was distinctly masculine in distribution and the legs showed hypertrichosis. Routine neurological examination gave normal findings.

*Laboratory Summary:* The patient was 29 per cent underweight and somewhat below her predicted lung volume. A fairly satisfactory basal rate was 13 per cent below prediction. The blood pressure was low and the $CO_2$ definitely below the normal. The urine volume was scanty, protein intake was inadequate, redisual nitrogen normal. Her sugar tolerance was 50 per cent below the normal. The blood showed a very marked lymphocytosis.

*Nose and Throat Examination:* The examiner demonstrated infected tonsillar remnants.

*Neurological Examination:* The examiner defined the condition as a manic depressive psychosis of the depressed type. There was no evidence of organic nerve lesion.

*Endermal Tests:* The patient gave a positive reaction to egg albumin.

*Radiography:* The skull showed the effects of the earlier trauma but was otherwise normal.

*Eye Examination:* The discs were yellowish, remaining findings normal.

*Discussion:* The clinical and laboratory study here point clearly to an ovarian failure. It was recommended that the patient have the infected tonsillar remnants removed, eggs omitted from the diet, and that endocrine therapy be followed. In view of her suicidal tendencies it was also recommended that she be placed under restraint.

A later report shows no real improvement in the condition, but glandular therapy was exhibited for only a short time.

CASE B-530. The patient was a delinquent girl of 19 with a history of hetero- and homo-sexuality, together with other sex perversions. She had also committed petty thefts and had presented other behavior problems. She had been committed at the age of 13, six years before her admission to the hospital. As she had become obese and had developed a number of possible endocrine stigmata, she was referred to this Clinic for study.

*Family History:* The patient was an orphan; there are a brother and sister who are entirely normal. The family history as recorded is not informative.

*Past History:* As a child she had minor ailments, removal of a tumor from the left leg, tonsillectomy and adenectomy. She complained of an occasional headache, rather frequent nose-bleed for a short time a year previously, and recently had had an abscessed tooth. The menstrual history was substantially normal, with establishment at the age of 13.

*Physical Examination:* The patient was a very well developed, somewhat obese girl of 19. The hair on the vertex was coarse and thick. The eyes were normal; the thyroid not palpable. The hands and feet were large and symmetrical. There was a distinct flattening of the normal thoracic curve upward from the fifth vertebra. She had considerable acne on the face and chest and a minor inguinal adenopathy. The body hair was abundant but approximated the female configuration. A routine neurological examination gave normal findings. Mentally she was found to be rather slow.

*Laboratory Summary:* The patient was 23 per cent overweight. An unsatisfactory basal test was 5 per cent above prediction, her true rate being unquestionably lower. The blood pressure was slightly low, the temperature slightly high. Alveolar $CO_2$ was a low normal. The urine was normal throughout; the phthalein test slightly low; the sugar tolerance half the normal level. The blood was lymphoid in type.

*Pelvic Examination* showed an introitus admitting two fingers; otherwise the findings were normal.

*Barany:* Static labyrinth showed an almost total lack of response to stimulation. This was felt to be congenital as a growth or a toxaemia would not be likely to destroy the function of the static branch of the 8th nerve before beginning to affect the cochleal branch.

*Neurological findings* were substantially normal. A possible nystagmus was recorded.

*Radiography:* The sella was normal and the thoracic spine normal. One infected tooth was disclosed.

*Cardiogram* was normal.

*Eye Examination:* The right disc was slightly yellowish; remaining findings were normal.

*Discussion:* The general picture here presented suggests an ovarian failure. Ovarian medication was recommended and the patient discharged. Eighteen months later she was again admitted. In the meantime, so far as we could ascertain, she had received no medication. The laboratory picture which she presented was substantially identical with that first recorded. She had attempted to diet, but had lowered her weight by less than 2 lbs. Under wise direction and suggestion her social status had improved. Certain of the behavior problems had become less serious and she was definitely on the way to rehabilitation. She was discharged with the strong recommendation that she be given the benefit of endocrine medication. A later report records definite general improvement.

A point of interest in this and the preceding case is the persistence of a sex appetite, albeit abnormal, in the presence of ovarian failure. We have had occasion to remark this many times and in many women with wholly normal heterosexuality we have recorded a marked libido persisting for years after demonstrable ovarian failure. Extreme cases are those in which castration is the cause of the hypogonadism, and even here a loss of sex appetite is by no means the invariable rule. A male case in the next group is possibly significant in this connection.

### GROUP III. CASTRATES

CASE B-42. The present case is particularly interesting as demonstrating the slight influence on the general picture which ablation of the testicles in adult years will produce. The patient had been operated upon eight years before for tuberculosis of the testicles by Dr. John H. Cunningham, through whose kindness and interest we were able to study this patient. At the time that the patient was 19 years of age he noted some irritation of the penis. There was a slight discharge and some burning on micturition. He was treated by several physicians for gonorrhea. Ultimately he consulted the referring physician, and the condition was diagnosed as a tuberculous state. One testicle was removed nine years ago, the patient being 25, and the second three months later. For some 15 years the patient has had a cough which is usually unproductive. He entered the hospital for a general survey and primarily, in a very gracious spirit of cooperation, to assist in the work of the Clinic.

*Family History:* The mother and two sisters died of tuberculosis; the remaining history not significant.

*Past History:* The patient reported measles and malaria, an earlier attack of jaundice, and the condition noted above. He had occasional attacks of vertigo, some obstruction of the right nostril, some loss of hearing in the right ear. He had a tendency to constipation and had lost about 20 lbs. since his operation. A tonsil and adenoid operation had been performed a year previously. The tuberculous condition had been apparently eradicated.

*Physical Examination:* The patient was well developed and somewhat underweight, the skin was somewhat dry, teeth showed much dentistry, breath sounds and vocal fremitus apparently somewhat increased on the right. Blood pressure was slightly low. The scrotum was empty. The knee jerks were reported as somewhat exaggerated and the cremasteric reflexes absent.

*Laboratory Summary:* The patient was 11 per cent underweight and the basal rate was 11 per cent below prediction. The somewhat low blood pressure was confirmed; the pulse rate and temperature were somewhat low. The urine presented an entirely normal picture. The phthalein output was normal. Sugar tolerance was normal. Blood constituents were normal. The blood showed a 4 per cent eosinophilia.

*Radiography* findings were normal throughout.

*Discussion:* At the time this patient was studied it was not possible for us to secure a number of the observations which have become routine in the later investigations. The significant feature of the laboratory picture is its relative normality, a borderline basal rate with somewhat low blood pressure being the only real departure from the normal. The subsequent history of this case is very striking and we believe worthy of record. At the time that the patient was seen his real difficulty lay in his profound mental depression. It was this condition rather than physical fatigability which had been progressively lowering his effort and lessening his ambition. After his operation he had returned to the small country town in which he had been born, giving up a varied and interesting career which involved

## TABLE XIX

| | Castrates | | | | Mumps | |
|---|---|---|---|---|---|---|
| Case Number | B-42 | S-197 | S-261 | S-1074 | B-103 | S-735 |
| Sex | M | F | F | F | F | M |
| Age (yrs.) | 34 | 42 | 59 | 68 | 20 | 40 |
| Height (cm.) | 169 | 164 | 167 | 160 | 155 | 175 |
| Weight (kgm.) | 52.9 | 60.7 | 62.8 | 51.8 | 47.0 | 66.9 |
| Weight Deviation (%) | −11 | +14 | +18 | −6 | −12 | −5 |
| Lung Volume Deviation (%) | −7 | −11 | −20 | −9 | −25 | +5 |
| Basal Rate Deviation (%) | −11 | −17 | −15 | −21 | −13 | −15 |
| Blood Pressure (mm.) | 106/62 | 120/82 | 128/52 | 124/62 | 104/72 | 106/58 |
| Pulse Rate (per min.) | 58 | 70 | 80 | 60 | 80 | 64 |
| Temperature (deg. F.) | 97.5 | 98.6 | 98.2 | 98.2 | 98.8 | 98.2 |
| Alveolar $CO_2$ (mm.) | 41 | 35 | 34 | 40 | 32 | 44 |
| Urine Volume (cc.) | 1150 | 1050 | 960 | 2000 | 720 | 1360 |
| Spec. Grav. | 1.022 | 1.014 | 1.026 | 1.015 | 1.012 | 1.018 |
| Albumin | 0 | 0 | 0 | + | 0 | 0 |
| Casts | 0 | 0 | 0 | 0 | 0 | 0 |
| Sugar | 0 | + | 0 | 0 | 0 | 0 |
| Total Nitrogen (gms.) | 10.64 | 7.13 | 11.07 | 11.85 | 8.46 | 7.28 |
| Residual Nitrogen (%) | 1.6 | 13.5 | 7.9 | 10.8 | 9.5 | 6.9 |
| Phen. Sulph. Phthal. (%) | 58 | 64 | 57 | 60 | 58 | 53 |
| Galac. Tol.— | | | | | | |
| Normal (gms.) | 30 | 40 | 30 | 30 | 40 | 30 |
| Observed (gms.) | 30 | 20 | 20 | 20 | 20 | 30 |
| Deviation (%) | +0 | −50 | −33 | −33 | −50 | +0 |
| Blood— | | | | | | |
| Non-Protein Nitrogen (mgm.) | 34 | 30 | 42 | 32 | 31 | 34 |
| Uric Acid (mgm.) | 2.8 | 3.0 | 3.8 | 2.6 | 4.0 | 3.7 |
| Sugar (mgm.) | 82 | 91 | 91 | 84 | 76 | 90 |
| Haemoglobin (%) | 90 | 90 | 95 | 90 | 85 | 80 |
| Erythrocytes ($10^6$) | 5.52 | 6.07 | 4.84 | 5.07 | 4.58 | 4.72 |
| Leucocytes ($10^3$) | 9.10 | 8.60 | 5.25 | 4.30 | 5.50 | 5.20 |
| Neutrophiles (%) | 68 | 38 | 47 | 67 | 60 | 59 |
| Lymphocytes (%) | 23 | 56 | 43 | 25 | 32 | 34 |
| Eosinophiles (%) | 4 | 1 | 5 | 1 | 1 | 5 |
| Monocytes (%) | 5 | 5 | 5 | 7 | 7 | 2 |
| Misc. (%) | 0 | 0 | 0 | 0 | 0 | 0 |

B-42 Male castrate (Tuberculosis of testicles).
S-197 Female, pre-menopause castrate before menopause age.
S-261 Female, pre-menopause castrate after menopause age.
S-1074 Female, post-menopause castrate after menopause age.
B-103 Oophoritis following mumps.

much foreign travel. He naturally resumed relations with the young people with whom he had grown up, and with his attractive personality and extremely interesting conversation he won the regard of one of the young women of the town. She was entirely willing to marry him, knowing in full his physical condition. Shortly after his visit to the hospital this plan was carried out. The patient found himself not only capable of erection but of intercourse with his wife which was entirely satisfactory to her. The psychological effect of this outcome was very striking. He resumed his outside interests shortly after his marriage, and moved to the West, where he organized and is conducting a most successful business in one of the larger cities. That the erectile power is not destroyed by castration after maturity is well known. This protocol is offered as a striking example both of the slight effect on the physical picture produced by castration, and the very definite influence on the patient's psychology produced by the conviction that a portion of his manhood remained in spite of his mutilating operation. The authors feel that a case such as this may explain some of the miracles which operative procedures are alleged to have wrought.

CASE S-197. This patient represents the results of castration in the pre-menopausal period studied before the menopause would normally have taken place. Her complaint on entrance was of failing vision in the right eye. She had suffered from this for the past six months. Since the initial onset of the condition there had been some improvement, but there remained an impression in her mind that the vision was circumscribed. Four years previously she had had a complete hysterectomy following which headaches from which she had previously suffered were improved. Three years previously she developed a feeling of soreness in the epigastric region, tenderness of the abdomen, and occasional vomiting spells.

*Family History* was entirely irrelevant.

*Past History:* The patient had mumps and chicken-pox in childhood, typhoid at 21, and scarlet fever 2 years ago. She has always had the headaches mentioned above. An examination of the eyes previous to her admission gave only normal results. She reported an occasional nose-bleed, recently some slight precordial pain, occasional slight palpitation. There was a tendency to constipation. The patient had been having hot flashes since her operation. The catamenia began at 14, was regular with diminished interval and somewhat profuse flow. There was continued flow for some six months prior to the operation which was necessitated by a fibroid tumor.

*Physical Examination* showed a well-developed and well-nourished woman; the skin was somewhat dry and wrinkled; there was slight lateral nystagmus in both eyes, not confirmed later, and slight epiphora; the majority of the teeth were missing; the tongue showed a slight tremor, the tonsils were enlarged but apparently not offending; there was a slight cardiac systolic murmur, tenderness in the iliac regions, and a few superficial varicosities on the extremities.

*Laboratory Summary:* The patient was 14 per cent overweight with a basal rate of —17 per cent and slightly low blood pressure. Alveolar $CO_2$ was low. The urine picture was normal except for the presence of a trace of sugar and a high residual nitrogen. Her sugar tolerance was half that of the uncastrated woman of her age. The blood constituents were normal. The blood was lymphoid in type.

*Radiography:* A gastro-intestinal series was normal. The shadow of the gall bladder was reported as slightly more dense than normal. The lungs showed some increased density.

*Eye Examination* showed a very slight enlargement of the blind spots and was otherwise normal.

*Discussion:* The patient presented a fairly typical picture of hypogonadism as we have come to recognize it by the study of female castrates. The blood pressure is a little high, but the patient is 42 years old and somewhat nervous. The basal rate and the sugar tolerance are at typical levels, while the low $CO_2$, as has already been noted, is a common finding in conditions depressing the activity of the ovaries. Subsequent to the examination the patient gave no evidence of gall bladder disease, suggested by the skiagram.

CASE S-261. This patient was castrated before the menopause and was examined by us after the age at which the menopause would naturally have occurred.

The patient's chief complaint was a marked fatigability. The condition dates back some 24 years in its onset, when the patient first began to exhibit a severe asthenia. Six years later a panehyterectomy was performed, the patient being 41 years of age at the time. Subsequent to the operation the asthenia increased and there were attacks of faintness and even of collapse. As the years have progressed these have become fewer in number and less severe. More recently she has developed some palpitation, tinnitus and vertigo.

*Family History:* The patient is one of ten children, seven of whom survive. One of the sisters has been studied in this Clinic and shown to be endocrinopathic (see Case B-37 in later "pluriglandular" paper). The family history was otherwise not remarkable.

*Past History:* The patient had measles three time in childhood, mumps at the age of 15, the operation already noted, and a submucous turbinate resection and a hemorrhoidectomy. She had severe headaches for a number of years, but recently they have been infrequent. She reports an abscess in the right ear 15 years ago. She was subject to head-colds. The teeth have caused a great deal of trouble. She complained of hoarseness and an irritating cough. She was subject to urinary frequency and, when unable to void, to incontinence. The catamenia was established at 13, the periods were regular and flow very profuse. Of late years she has been troubled with vulval pruritus.

*Physical Examination:* The patient was a well-developed, somewhat obese woman of 59; the hair was dry and scanty and the scalp showed areas of eczema. The skin was dry and there were certain pigmented areas on different parts of the body. The remaining examination showed only a slight cardiac irregularity.

*Laboratory Summary:* The patient was 18 per cent overweight. The basal rate was —15 per cent. The diastolic blood pressure was definitely low, the systolic slightly so, the pulse was somewhat rapid. Alveolar $CO_2$ was below the normal. The urine was negative. Nitrogen partition was normal. The sugar tolerance was at the prepubertal level of 20 grams. The non-protein nitrogen of the blood was above the normal. There was a definite lymphocytosis and a 5 per cent eosinophilia.

*Eye Examination:* Entirely normal.

*Radiography:* The skull was somewhat thick, the frontal sinuses obscured. There was an atheroma of the aortic arch and some pulmonary fibrosis. Remaining findings were normal.

*Skin Examination* defines seborrhea, eczema of the scalp and senile changes in the skin.

*Barany:* This test gave evidence of slight irritation, possibly toxic in origin.

*Neurological Examination:* No evidence of organic nerve lesion was secured. The patient was highly neurotic.

*Discussion:* The picture here conforms in significant findings with those to be predicted from a complete castration.

CASE S-1074. This patient represents a study of a woman castrated a number of years after the menopause. Her chief complaint was of eczema which involved the hands but no other parts of the body. This condition had obtained for a number of years, being more marked in the winter time and much better in the summer. The patient stated that she washed her hands fifty times a day in plain water and three times daily with a medicated soap.

*Family History:* Both the parents were arthritic. The mother died of cancer and a paternal uncle was psychotic. The patient was an only child.

*Past History:* She had the minor ailments in childhood, scarlet fever at 26 without sequelae, and was subject to a severe dysentery every summer during young girlhood. Fifteen years ago she developed a cardiac condition which necessitated her remaining in bed for three months. Twelve years previously she had had an appendectomy, and within the year a pan-hysterectomy had been performed for a large fibroid tumor, the patient then being 67 years of age. She complained of occasional headache, a long-standing post-nasal catarrh; she had had a submucous turbinate resection 25 years before, removal of several abscessed teeth and had one tooth still discharging. During young girlhood she was constipated, and has had a tendency to this condition throughout her life. The menstrual history was entirely normal, including an uneventful menopause at 50.

*Physical Examination:* The patient was an elderly woman seemingly in good physical condition and good nutritional balance. The teeth showed much dentistry; the nipples were undeveloped, there was a reduplication of the first heart sound, both kidneys were low, the right kidney movable, hands showed evidence of eczematous involvement, and there was some anterior curve to the dorsal spine, but the station and gait were very good for one of the patient's age.

*Laboratory Summary:* The patient was 6 per cent underweight. The basal rate was —21 per cent, with relatively a somewhat low blood pressure. The $CO_2$ was normal. The urine volume was ample, the urine contained albumin. The residual nitrogen was high. The sugar tolerance was at the prepubertal level of 20 grams. Blood constituents and blood morphology were normal. A long series of endermal tests showed the patient not reactive to a large number of proteins.

*Cardiogram* was normal.

*Radiography:* The heart was not enlarged; the sinuses and skull were normal; the teeth showed no infection, but there were numerous

bulbous roots consistent with exostoses. The lungs showed increased density and fine mottling at the apices.

*Chest Examination:* Normal findings were reported.

*Eye Examination:* There was an undefined central scotoma in the left eye which the examiner believed was due to retinal hemorrhage. Remaining findings were normal.

*Discussion:* The picture here presented is that of a woman of 68 in surprisingly good general physical condition. The lowered basal rate and sugar tolerance are the only real indices of endocrine disturbance. The probability would seem to be that during the years which had elapsed since the menopause (18), the patient had so far adjusted that her subsequent castration did not produce such marked changes as are normally observed in younger women.

### GROUP IV. GONAD FAILURE FOLLOWING MUMPS COMPLICATED BY GONAD INVOLVEMENT

CASE B-103. OÖPHORITIS. The patient's chief complaint was of abdominal pain over the ovarian region. A few weeks earlier she had had an attack of the mumps and since her convalescence had become markedly asthenic and nervous. The pain was greater over the right ovary region, but there was a steady dull ache over the entire lower abdomen.

*Family History:* The mother and aunt had had pulmonary tuberculosis. One sister had some condition, the nature of which was unknown to the patient, involving the cervical lymphatics.

*Past History:* In addition to mumps the patient had had chickenpox, measles and pertussis. Eight years previously, at the age of 12, the appendix had been removed and there was a partial resection of a cystic right ovary. The patient matured in the following year, and her subsequent menstrual history has been entirely normal. The remaining history showed a marked constipation, a sensitivity to fish, and a vaginal discharge for the preceding two years.

*Physical Examination:* The patient was a well-developed but somewhat undernourished girl of 20. The parotid and submaxillary glands were somewhat hypertrophied and tender. She had a slight bilateral nasal obstruction. The breasts were of the prepubertal type. Marked hypersensitiveness was elicited over both ovaries, more pronounced on the right. Hair was abundant but normal in distribution.

*Laboratory Summary:* The patient was 12 per cent underweight and 13 per cent below her predicted lung volume. The blood pressure was low and the $CO_2$ definitely below normal. The urine was somewhat scanty, otherwise normal. The residual nitrogen fraction was high. The sugar tolerance was half the normal. Blood uric acid was somewhat high, blood sugar slightly below normal. The blood morphology was normal.

*Radiography:* The skull and chest were normal. There was no evidence of sub-sternal enlargement. The barium enema disclosed no disorder of the colon.

*Neurological Examination* disclosed no evidence of any organic neurological condition.

*Bacteriological Examination:* The vaginal smear showed no pathogenic organisms.

*Pelvic Examination:* Reported as normal except for tenderness as already noted.

*Discussion:* The picture presented here is typical of gonad failure. The coincidence of the patient's mumps and the development of her symptoms would make it probable that an oöphoritis complicating the mumps was responsible for the lowered functional activity. Ovarian medication was recommended. A recent report states that the patient improved definitely, later married, and has two children. Our study here was of an acute condition which has certainly been corrected—probably as the outcome of natural curative agencies.

CASE B-457. The patient's chief complaint was of fatigability and asthenia, with occasional periods of extreme mental activity. He also complained of headache and insomnia. He had had orchitis at the age of 15 following a severe attack of mumps. He entered college at 19, but found it difficult to carry on his academic work because of fatigability. He stated that by concentration he was able to work very rapidly, but only for a brief space of time. He dropped out of college in the middle of his second year at the suggestion of the authorities. Since that time he had tried a variety of employments, in all of which he had failed. Shortly after leaving college he had a fall down an elevator shaft; was in bed for a month and incapacitated for work for six months. The fall produced only muscular injury. He reiterated a symptom of a feeling of pressure in the head, and to this he ascribed most of his difficulties. He also had suffered greatly from insomnia and had taken large quantities of various hypnotics to produce sleep. He had had extensive medical contacts and on several occasions had taken somewhat promiscuous endocrine therapy.

*Family History:* The patient was an only child. On the paternal side of the family are numerous neurotics; the father is himself extremely nervous and irritable.

*Past History:* The patient reported mumps as above, measles and whooping cough, the injury to the back already noted, a streptococcus infection of the neck 13 years earlier, a tendency to bronchitis, and for the last 30 years hay fever during the ragweed season. He complained of attacks of acute indigestion and of constipation. He gave a history of nocturia and a feeling of bladder irritation.

*Physical Examination:* The patient was a well-developed and fairly well-nourished man of 40. We quote from the examiner's record: "It was very difficult at first to elicit definite information. The patient seemed to have a very much retarded psychomotor activity and found it very difficult to remember things. He seemed very sleepy and would apparently fall off to sleep at intervals in the questioning. As the examination progressed, however, he became brighter and more alert, and at the end of about two hours became much aroused and excited over his general condition." The hair on the vertex was thin; the teeth were poor and showed much dentistry; heart action was slow but regular; the left testicle was the size of a large egg, the right slightly smaller; the knee jerks were hyperactive.

*Laboratory Summary:* The patient was 5 per cent underweight; his basal rate was —15 per cent; blood pressure somewhat low. The urine was normal, as was nitrogen partition. Sugar tolerance was

normal. Chemical blood constituents were normal. Blood morphology study showed a slightly low haemoglobin, a slight relative lymphocytosis, and a 5 per cent eosinophilia, undoubtedly referable to his hay fever.

*Radiography:* The chest was normal, as was the sella; large sphenoid cells were noted.

*Audiogram:* The aural acuity was normal.

*Neurological Examination:* The patient had been defined elsewhere as a psychoneurotic. The examiner found no evidence of organic nervous disorder.

*Eye Examination:* The disc margins were indistinct and the discs themselves were yellowish. The blind spots were slightly enlarged.

*Discussion:* In general the patient presented a normal picture. His nervous instability induced a lack of cooperation which prevented the performance of a number of desirable tests. Among these was a psychiatric examination. The patient was not entirely ingenuous, being overwilling to offer massive detail in regard to his presenting difficulties with a compensatory reticence about such matters as his sex life. The laboratory picture which he presented is identical with that produced by castration of the male in adult years. In the light of present knowledge we are not prepared to ascribe his nervous instability to this condition, preferring to regard the two as existing coincidently.

## TABLE XX

| | Sterility | Normal Pregnancy | | | |
|---|---|---|---|---|---|
| Case Number | S-837 | M-8 | | M-9 | |
| Time | — | early | late | early | late |
| Parous | 0 | 1 | | 3 | |
| Age (yrs) | 22 | 29 | 29 | 34 | 35 |
| Height (cm) | 162.0 | 157 | 157 | 177.5 | 177.5 |
| Weight (kgm.) | 57.8 | 55.2 | 64.1 | 88.7 | 92.6 |
| Weight Deviation (%) | +1 | +6 | +23 | +24 | +32 |
| Lung Volume Deviation (%) | −34 | — | — | −15 | −7 |
| Basal Rate Deviation (%) | −9 | +3 | −6 | −7 | −5 |
| Blood Pressure (mm.) | 92/60 | 94/70 | 102/74 | 108/66 | 100/30 |
| Pulse Rate (per min.) | 72 | 90 | 88 | 70 | 80 |
| Temperature (deg. F.) | 98.0 | 98.2 | 98.1 | 97.0 | 97.9 |
| Alveolar $CO_2$ (mm.) | 44 | 36 | 33 | 35 | 34 |
| Urine Volume (cc.) | 520 | 910 | 1500 | 1200 | 3300 |
| Spec. Grav. | 1.033 | 1.021 | 1.015 | 1.016 | 1.010 |
| Albumin | 0 | + | 0 | + | 0 |
| Casts | 0 | 0 | 0 | 0 | 0 |
| Sugar | 0 | 0 | + | 0 | 0 |
| Total Nitrogen (gms.) | 7.28 | 6.23 | 7.42 | 9.26 | 9.65 |
| Residual Nitrogen (%) | 8.0 | 7.4 | 9.1 | 4.6 | 4.7 |
| Phen. Sulph. Phthal (%) | 62 | — | — | — | — |
| Galac. Tol.— | | | | | |
| Normal (gms.) | 40 | 40 | 40 | 40 | 40 |
| Observed (gms.) | < Normal | 30 | 20 | 30 | 20 |
| Deviation (%) | | −25 | −50 | −25 | −50 |
| Blood— | | | | | |
| Non-Protein Nitrogen (mgm.) | 26 | — | — | 28 | 28 |
| Uric Acid (mgm.) | 3.1 | — | — | 3.5 | 3.5 |
| Sugar (mgm.) | 86 | 100 | 100 | 100 | 91 |
| Haemoglobin (%) | 85 | | | 85 | 75 |
| Erythrocytes ($10^6$) | 4.21 | | | 4.25 | 3.98 |
| Leucocytes ($10^3$) | 5.80 | | | 8.80 | 8.30 |
| Neutrophiles (%) | 61 | Recorded as | | 70 | 63 |
| Lymphocytes (%) | 38 | normal | | 22 | 32 |
| Eosinophiles (%) | 0 | | | 1 | 0 |
| Monocytes (%) | 1 | | | 7 | 5 |
| Misc. (%) | 0 | | | 0 | 0 |

GROUP V. STERILITY

CASE S-837. The patient's chief complaint as presented was a decalcification of the teeth. The condition had obtained for the last six months and the patient had been urged by her dentist to have the cause of the condition investigated. An additional factor was a sterility which the patient hoped to overcome. She had been married for something more than two years without conceiving. By inference, at least, the husband had been eliminated from the etiologic equation.

*Family History* was entirely irrelevant.

*Past History:* The patient had had minor ailments, influenza at the time of the epidemic, and a tonsil and adenoid operation at the age of 7. For the past few years she had suffered from frontal headaches. The catamenia began at 14, had always been irregular, with increase in the interval, while the flow was definitely scanty. The remaining history as given was not informative. The patient was distinctly egocentric, irritable, and incooperative, which naturally were matters of record and not of the patient's report.

*Physical Examination:* The patient was a well-developed and well-nourished woman of 22. There were a small sebaceous cyst on the right side of the vertex, a few palpable anterior cervical glands, a slightly enlarged thyroid. The remaining examination was not significant.

*Laboratory Summary:* The patient was within one per cent of her predicted weight. The basal rate was reported as —9 per cent, but the conditions of the test were not entirely satisfactory and the true value was undoubtedly somewhat lower. The blood pressure was low. Alveolar $CO_2$ was normal. The urine was scanty and concentrated, the protein intake somewhat low, the residual nitrogen fraction normal. Blood chemistry was normal. The blood showed a slight secondary anaemia and a relative lymphocytosis. The patient did not complete the sugar tolerance test, but the partial examination showed it to be below the normal.

*Pelvic Examination:* This had been performed elsewhere and was reported as normal.

*Blood Calcium:* The test showed 11.5 mgm., a slightly high value.

*Discussion:* The preparation of the case was patently incomplete. It was felt, however, that the picture was generally suggestive of a primary ovarian failure. Ovarian medication was recommended, and this was followed out. Within a comparatively short time the patient became pregnant and was later confined of a normal child. We are not informed as to the subsequent condition of the teeth, since contact with the patient was lost.

In a series of gonad failures which we have investigated a number of the subjects have given a history of sterility. During the earlier studies it was impossible to resolve this question satisfactorily, but more recently a clinic has been established for the specific study of this condition. Preliminary notices of the work have already appeared (56) and the results of the investigation will be reported elsewhere. In brief, it involves a very thorough clinical and laboratory study of both partners. The case recorded above illustrates the apparent correction of a sterility occurring more or less fortuitously, as the study of the patient was most incomplete and there were no available data for the male other than a general statement.

GROUP VI. NORMAL PREGNANCY

The status of ovarian function during pregnancy is a moot point and has already been touched upon in an earlier portion of this paper. For a number of years past one of us has been conducting somewhat extensive studies on the laboratory and clinical findings during the progress of normal pregnancy. The data from two such cases are offered here as a text for general discussion.

CASE M-8. This patient was a woman of 29 who had been married for several years and who had just become pregnant. Through the courtesy of the patient's physician and her own gracious cooperation we were able to make repeated studies at intervals of substantially two weeks, during the last twenty-six weeks of the pregnancy. Two typical protocols have been selected and the laboratory data incorporated in the table above. These may be briefly reviewed. The patient was a young woman of 29, in good general physical condition. The family history was not significant; her own past history showed no important departures from the normal, and the physical findings were substantially normal. At the time of the first examination, which was twenty-six weeks before delivery, she was 6 per cent overweight, with a basal rate reported as +3 per cent. This latter was probably slighty high, as a week later she gave the value of —5 per cent. The blood pressure was low, pulse somewhat rapid, alveolar carbon dioxide a low normal value. The urine was a low normal in volume and contained a trace of albumin. Her protein intake was below a maintenance level, as gauged by the amount eliminated. The residual nitrogen fraction was normal. Her sugar tolerance was 10 grams below prediction. Of the blood constituents only the sugar was determined, the level obtained being normal. The blood morphology was investigated elsewhere and was reported to us as normal.

The second report was secured some two weeks before delivery. The patient had increased nearly 9 kgm. in weight and was now 23 per cent above prediction. The basal rate was —6 per cent, the blood pressure higher, but still at a hypotensive level. The pulse remained somewhat rapid. The $CO_2$ had dropped to a level below the normal. The urine volume was ample, albumin had disappeared, but a trace of sugar was recorded. It may be said, parenthetically, that a slight glycosuria is frequently recorded during the course of pregnancy. The protein intake had apparently improved slightly, but was still at a sub-maintenance level. The residual fraction was just above the conventional normal. Her sugar tolerance had dropped to 20 grams, the level of prepubertal years, of castration and of severe functional failure. Again only the blood sugar was recorded, and that at the same normal level. The blood morphology was again reported as normal. Discussion of this case will be postponed until the data of the second case have been considered.

CASE M-9. In the study of this case we were peculiarly fortunate, as we had records of the patient's functional leval prior to conception and were enabled, through her cooperation, to carry out a continued study throughout the entire course of her pregnancy. The data secured before conception showed a moderate degree of obesity (+14 per cent), a normal basal rate with normal $CO_2$, a normal blood and urine picture, and a sugar tolerance at 40 grams, the normal level for a healthy woman of her age in a state of sexual rest. The first test recorded in the table was secured in the thirtieth week before delivery. The patient had increased in weight materially and was

24 per cent above prediction. The basal rate was —7 per cent, the blood pressure somewhat low, the alveolar carbon dioxide at a low normal level. The urine picture was substantially normal, except for a very slight trace of albumin, an observation of frequent occurrence in this condition. The sugar tolerance was 25 per cent below prediction. The blood composition was normal, the blood morphology indicating a slight anaemic tendency. The leucocytic formula was normal. The last test was performed during the third week before delivery. The patient had added nearly four kgm. to her weight and was now 32 per cent above prediction. The lung volume had improved, a rather usual occurrence, as has already been noted by one of us (44). The basal rate deviation was —5 per cent, the blood pressure still lower than before, the alveolar carbon dioxide slightly lower. The urine volume had increased and was in excess of three liters. The remaining findings were entirely normal. The sugar tolerance had fallen to the characteristic 20-gram level, the blood composition continued normal, the anaemia was somewhat more pronounced. There was an absolute increase in the lymphocytes, which, however, were within normal limits.

*Discussion:* The basal rate changes during pregnancy have already been recorded by one of us (22) in a series of cases, and the findings have been confirmed in substance by careful studies on individual patients. During the early stages of pregnancy there is a tendency for the basal rate to fall somewhat below prediction, while the terminal phase reaches a level about the same amount above. Both values (—8 to +8 per cent) fall within conventional normal limits. The curve of change, however, in any given case shows considerable variation in the individual measurements. As earlier noted (23) Sandiford has suggested that this increase depends upon the added surface caused by foetal growth. As this assumption involves uncertain extrapolations and is based upon the study of a single case, too much weight should not be given to it. The fact remains, however, that for some cause not yet clearly determined, the basal rate increases during pregnancy an average of 16 per cent above the prediction based upon the usual conventional standards. This increase will obscure any lowering of the mother's individual basal as dissociated from that of the highly active protoplasmic mass of the foetus. A lengthy discussion may not be undertaken here. It may be said, however, that if allowance be made for the superimposed effect of pregnancy with its unknown mechanism, the maternal basal rates are not inconsistent with the slight depressions incident to ovarian failure.

The lowering of the alveolar carbon dioxide without any evidence of an existing acidosis parallels exactly the frequent observation in ovarian failure. The glycosuria of pregnancy (and this is a glycosuria, as has been clearly demonstrated) corresponds with the similar phenomenon observed in numerous other conditions, among which primary ovarian failure is numbered.

The lowering of the galactose tolerance parallels exactly the changes produced by the mild and by severe functional failure and castration.

To summarzie then, the laboratory picture presented by the pregnant woman parallels closely that of non-pregnant female exhibiting a lowered endocrine activity of the ovaries. We do not feel that the case is proven, as it is recognized that pituitary changes take place during this interesting physiological event. With marked posterior lobe overactivity, however, the tolerance should sink below 20 grams, which in our somewhat extended experience has never been the case. Furthermore, the tolerance lowering appears very early

in the pregnancy and at a time when profound changes of pituitary activity are neither demonstrable nor probable. Teleology would support the general thesis. We offer the observed facts and a possible interpretation which we regard as probable but certainly not established.

TABLE XXI

| | Psychosis | | | | Deaf | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | 4 | 5 |
| Case Number | B-621 | B-374 | S-411 | S-1054 | S-1690 | S-813 |
| Sex | F | F | F | F | F | F |
| Age (yrs.) | 28 | 36 | 21 | 23 | 20 | 29 |
| Height (cm.) | 155.6 | 159.3 | 158.0 | 158.0 | 163.0 | 150.0 |
| Weight (kgm.) | 37.3 | 56.1 | 55.2 | 62.9 | 56.5 | 57.5 |
| Weight Deviation (%) | −30 | −6 | +2 | +14 | +1 | +9 |
| Lung Volume Deviation (%) | +26 | −6 | −19 | −5 | +9 | −20 |
| Basal Rate Deviation (%) | −22 | −19 | −11 | −14 | −12 | −14 |
| Blood Pressure (mm.) | 98/60 | 100/62 | 98/72 | 112/68 | 90/48 | 100/61 |
| Pulse Rate (per min.) | 76 | 70 | 76 | 74 | 70 | 68 |
| Temperature (deg. F.) | 98.4 | 97.5 | 98.7 | 98.4 | 98.8 | 98.2 |
| Alveolar $CO_2$ (mm.) | 36 | 40 | 31 | 40 | 39 | 41 |
| Urine Volume (cc.) | 1340 | 540 | 2430 | 1500 | 1090 | 740 |
| Spec. Grav. | 1.015 | 1.021 | 1.011 | 1.016 | 1.017 | 1.019 |
| Albumin | 0 | + | 0 | 0 | 0 | 0 |
| Casts | 0 | 0 | 0 | 0 | 0 | 0 |
| Sugar | + | 0 | 0 | 0 | 0 | 0 |
| Total Nitrogen (gms.) | 6.56 | 6.00 | 14.36 | 8.20 | 11.00 | 6.14 |
| Residual Nitrogen (%) | 13.5 | 9.5 | 13.5 | 8.9 | 8.4 | 11.2 |
| Phen. Sulph. Phthal. (%) | 65 | 64 | 65 | 56 | 57 | 45 |
| Galac. Tol.— | | | | | | |
| Normal (gms.) | 40 | 40 | 40 | 40 | 40 | 40 |
| Observed (gms.) | 20 | 30 | 20 | 20 | 20 | 20 |
| Deviation (%) | −50 | −25 | −50 | −50 | −50 | −50 |
| Blood— | | | | | | |
| Non-Protein Nitrogen (mgm.) | 29 | 33 | 32 | 26 | 34 | 31 |
| Uric Acid (mgm.) | 4.1 | 2.9 | – | 2.7 | 3.3 | 3.7 |
| Sugar (mgm.) | 70 | 90 | 100 | 80 | 100 | 95 |
| Haemoglobin (%) | 90 | 75 | 95 | 70 | 96 | 80 |
| Erythrocytes ($10^6$) | 4.98 | 4.03 | 5.62 | 3.80 | 5.64 | 4.71 |
| Leucocytes ($10^3$) | 11.50 | 5.25 | 9.80 | 6.80 | 7.60 | 11.80 |
| Neutrophiles (%) | 66 | 51 | 61 | 51 | 56 | 60 |
| Lymphocytes (%) | 29 | 42 | 32 | 39 | 42 | 29 |
| Eosinophiles (%) | 1 | 4 | 1 | 2 | 1 | 2 |
| Monocytes (%) | 4 | 3 | 6 | 8 | 1 | 7 |
| Misc. (%) | 0 | 0 | 0 | 0 | 0 | 2 |

### GROUP VII. PSYCHOSES

The possible association of mental disease with endocrine imbalance is probably more generally accepted in connection with changing gonadal activity than in any other potential endocrine manifestation. The puerperal psychoses, the existence of which, it is true, is denied by many, the involution psychoses of the menopause, and possibly other types of mental disturbance appearing concomitantly with evidence of disturbed ovarian function, are cases in point. As we have discussed certain psychotic conditions appearing coincidently with aberrations of both the pituitary and the thyroid, it seems appropriate to review a few of these cases in which a psychosis and a primary gonad failure occur concurrently.

CASE B-621. The patient was admitted to the clinic offering as a chief complaint epileptic seizures accompanied by vague abdominal distress. The history of the epilepsy dated back 21 years, at which time the patient was 7 years of age. She had had scarlet fever during this year, but the seizures had already manifested themselves prior to this event. Up to the time of the catamenia, which occurred

at 13, they came at substantially monthly intervals. Since that time they have come at irregular periods, the quiescent interval, however, tending to be greater than in the early years. The abdominal condition had developed only a few months previously and apparently was wholly independent of the epileptic attacks. She described this condition as a definite pain at the left of the umbilicus and which radiated upward. It varied greatly in severity and in the duration of the attacks.

*Family History:* The patient has one brother who is normal and healthy. The family history is entirely irrelevant.

*Past History:* The patient reported the minor ailments of childhood, scarlet fever at 7, as noted above; a tonsillectomy and adenectomy and an appendectomy. Some years before admission she attempted to commit suicide by drinking iodine, and in addition to this there were two later psychotic episodes requiring restraint in an institution. She reported severe headaches with her epilepsy during the earlier years only. She was subject to palpitation, was constipated and complained of frequent attacks of indigestion. The menses were established at 13 and were regular but somewhat scanty. She has always been much underweight. The girl was a very simple-minded, immature individual whose presenting difficulty had caused a marked degree of isolation. Her life was very narrow and her mother, her sole associate. There has been a constant fear in later years that the mother would die and leave her alone, in which event she planned to die also.

*Physical Examination:* The patient was a fairly developed but much undernourished woman of 28. The lips were slightly bluish, the teeth in poor dental repair and several missing. The breasts were small and somewhat undeveloped; the heart, lungs and abdomen were normal, the knee jerks were hyperactive, and the remainding findings substantially normal.

*Laboratory Summary:* At the time of examination the patient was 30 per cent underweight, but definitely above her predicted lung volume. The basal rate was —22 per cent, the blood pressure definitely low, $CO_2$ a low normal. A trace of sugar was recorded in the urine, which was otherwise negative. The protein intake was below a maintenance level. The residual nitrogen fraction was very high. The sugar tolerance was half the normal. Blood uric acid was high and blood sugar low. There was a slight leucocytosis and a normal leucocytic formula. A report from the Boston Psychopathic Hospital,* made three years earlier, showed comparable values for the blood and urine findings and a basal rate very much higher. This latter was undoubtedly not the patient's true level. A second report from the Psychopathic Hospital of an admission a few months earlier than her admission here was again confirmatory as to the blood and urine findings. The basal rate was much lower than before, but still above prediction, and undoubtedly not representative of the patient's true basal rate.

*Nose and Throat Examination* gave normal findings.

*Radiography:* The heart, lungs, skull, sinuses and sella were all normal. The teeth showed no focal infections, but one retained root was demonstrated. A gastro-intestinal series was normal.

*Neurological Examination:* The examiner found no evidence of organic disease. He defined the condition as a true epilepsy.

*We take much pleasure in acknowledging our indebtedness for this and many similar courtesies.

*Pelvic Examination:* The patient showed a somewhat excessive hair growth; the examination was otherwise not informatory.

*Eye Examination* showed slightly enlarged blind spots, but otherwise no abnormality.

*Spinal Fluid* was reported to us as normal.

*Intelligence Quotient* was reported to us as 86.

*Discussion:* At the time of the first admission to the Psychopathic Hospital she was discharged with a diagnosis of psychosis with epilepsy. Re-examination a few months before her entrance to this Clinic disclosed epilepsy without psychosis. The laboratory picture here presented by the patient was consistent with a primary ovarian failure, and she was discharged with the diagnosis of hypogonadism with epilepsy. The question of existing psychosis was left in abeyance. Under the direction of one of us she was treated with follicular hormone and in a few weeks her general condition had improved materially. The basal rate had become —10 per cent, the blood pressure had increased to 106, the sugar tolerance was normal at 40 grams, the blood uric acid had fallen to 3.3, and the blood sugar increased to 91 mgm. She still showed high residual nitrogen in the urine. In so short a space of time it was impossible to say what influence this improvement of her functional level could have on her major difficulty. Her general condition was certainly improved at the time of her admission for the second study.

CASE B-374. The patient's chief complaint as given by herself was indigestion, from which she had suffered for about three years, with pain apparently both in the stomach and the abdomen, though the patient's description was not clear cut. Two years previously she had been for nearly a year at the Boston Psychopathic Hospital and been discharged as unimproved, with a diagnosis of dementia praecox. The first mental deviation was noted at the age of 18 by her family, when she began making remarks which were in nowise germane to the situation or to current conversation. Subsequently she graduated from college, making the Phi Beta Kappa. Following graduation, she taught in several high schools, but a gradually increasing repugnance to this work led her to discontinue it after two or three years. She was decidedly erratic during this period. She then took a course in a business college and subsequent to this was employed in a variety of business positions, including some newspaper work. She was not successful in any of these endeavors, and ultimately she went into the missionary field. Here erotic tendencies developed and she was brought back to Boston and placed in the Psychopatic Hospital, where she remained for about a year, as noted above. From that time until her entry into this Clinic, some 2½ years later, she had remained with her family, showing steady downward progress in the trend of her psychosis.

*Family History:* The patient was one of a large family, the general history of which was not significant.

*Past History:* She reported only minor ailments, an earlier otitis media and an occasional headache. The bowels were irregular. The menstrual history was not remarkable, except for very scanty periods. The remaining history was not significant, and in some respects was independable.

*Physical Examination:* The patient was a well-developed and nourished woman of 36, oriented as to environment and time. The

hair was normal in amount and distribution. The face showed a marked degree of brownish pigmentation, simulating the "mask of pregnancy." The breath was foul, the teeth in fair condition only. Fusiform papillæ on the anterior two-thirds of the tongue were very prominent and the glossal margin showed numerous teeth impressions. There was no thyroid enlargement. The remaining examination, including routine neurological observations, was not informative.

*Laboratory Summary:* The patient was 6 per cent underweight. The basal rate was 19 per cent below prediction, with very low blood pressure. The urine volume was scanty; albumin was recorded. The protein intake was apparently below a maintenance level; the residual nitrogen fraction was high. The sugar tolerance was 25 per cent below the normal. The blood was lymphoid in type; there was a 4 per cent œsinophilia and a secondary anæmia.

*Eye Examination:* The patient showed some symmetrical contraction of form and color fields.

*Neurological Examination:* The examiner defined a psychosis, probably a dementia præcox.

*Radiography:* Gastro-intestinal examination disclosed no abnormalities, except for probable disease in the appendix.

*Pelvic Examination* disclosed no abnormality.

*Bacteriological Examination:* A vaginal smear was normal.

*Discussion:* The general picture here is consistent with ovarian failure. The erotic element in the patient's complex is entirely consistent with this condition, as has been recorded elsewhere in this paper. That the psychotic condition is directly connected with the endocrine state is not a supportable thesis with such information as we have at present. Ovarian therapy was recommended, together with the necessary steps to correct existing difficulties, such as the anæmia and the pathological appendix. The subsequent history of this case is unknown to us.

CASE S-411 AND S-1054. The patient gave her chief complaint as a nervous breakdown. The more complete history was received through the courtesy of the referring physician, who stated that the patient had a brief psychotic attack prior to 1922, from which she recovered spontaneously. Again early in that year there was a period of depression which led to her commitment to the Boston Psychopathic Hospital, from which she was transferred to the Wiswall Sanitarium in February. The patient was excited, noisy and destructive and required occasional tube feeding. She remained in this condition for several months. There was a gradual diminution of the excited phase, with brief recurrence at the time of her periods. She gradually declined into an apathetic state and five months after her admission she cleared very rapidly, and in July of 1922 was sent home on a trial visit. She was readmitted on May 7, 1923, having lived an entirely normal life up to within a few days of her admission. She went through substantially the same cycle and was sent out on November, 1923. In May, 1924, she was again admitted, ran the same course of symptoms, and was sent home in September. The diagnosis established was that of a manic depressive psychosis. She was admitted here for study in late September of 1924.

*Family History* was not relevant. The patient is one of six children.

*Past History:* She reported measles, scarlet fever and chickenpox in childhood. The remaining history was entirely irrelevant, including that of the catamenia.

*Physical Examination:* The patient was well developed and nourished, the eyelids were inflamed, teeth were irregular and showed many fillings, there was a possible slight thyroid enlargement, the breasts were small and undeveloped, there was much hair on the chest and legs, and the pubic hair assumed the male configuration. The remaining findings were normal.

*Laboratory Summary:* The patient was within 2 per cent of her predicted weight. The basal rate was —11 per cent, blood pressure definitely low, $CO_2$ substantially below the normal. The urine volume was large, protein intake high, residual nitrogen much above the normal. The sugar tolerance was half the normal. Blood chemistry and blood morphology were substantially normal.

*Neurological Examination* gave no evidence of organic nervous disease.

*Discussion:* The patient presented a clear-cut picture of ovarian failure, with practically all of the evidences which we have learned to associate with this condition. Ovarian medication was advised.

Eighteen months later the patient was returned to us for further study. There had been one additional attack which had run the same course as the earlier seizures. She had had a series of boils in the preceding winter; the remaining history was not striking. She stated, however, that she had been under osteopathic and chiropractic treatment and had not followed the endocrine medication. The physical examination confirmed the earlier findings. There was, if anything, an increased hair growth, the external genitalia were essentially female in character and well developed. The recorded blood pressure was low. Laboratory examination showed an increase in weight of nearly 8 kgm. The basal rate was —14 per cent, the blood pressure at this time was higher than that recorded by the House Officer, but still low; the pulse was normal, as before. The urine volume was now more nearly normal; her protein intake had been cut down, but was still above maintenance. The residual nitrogen fraction was at the upper borderline of the normal. The sugar tolerance was unchanged and was half the normal. Blood composition was normal. The patient had developed a secondary anæmia and a relative lymphocytosis. Skiagrams taken at this time showed a normal sella and sinuses and a suggestion of convolution impressions on the inner table. A pelvic examination disclosed no abnormalities. The eye examination showed a very slight enlargement of the blind spots.

*Discussion:* The second test was highly interesting and gave confirmation of the results of the first examination in an untreated patient. Again ovarian medication was strongly recommended at the time of the patient's discharge. We are advised that it has been followed (10 grains t. i. d.), and that while the patient has had a recurrence the duration of the psychotic period has been greatly lessened. Medication is being continued.

### GROUP VIII. DEAFNESS

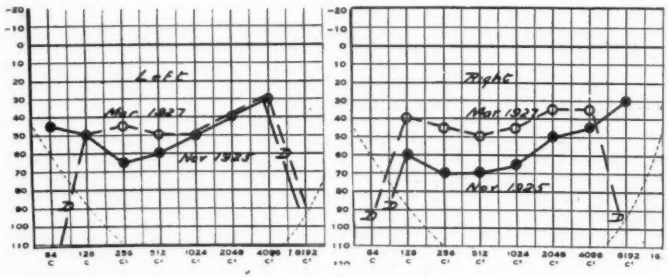
CASE S-813. The patient was a girl of 29, complaining of an increasing deafness in the left ear and a stationary loss in the right. As a child her hearing was normal. Impaired acuity was first noted at the age of 14, and then only in the right ear. At the age of 24

she found that the left ear had become involved, and this second condition had been progressive since that time. There was neither tinnitus nor paracusis.

*Family History* was not relevant.

*Past History:* The patient reported all of the minor ailments of childhood at an early age. She had influenza at the time of the epidemic, her age then being 22. In addition, she had had an appendectomy, with a later laparotomy for lysis of adhesions; two tonsillectomies and a dilatation and currettage operation for painful menstruation at about the time the second ear became involved. She complained of dull headaches, vertigo, susceptibility to colds, an abscess in the throat in 1910, and a fullness of the neck in the neighborhood of the thyroid. During the past three years she has become fatigable. She was markedly constipated and for a period of four years prior to her curettage she suffered from vomiting and pain in the right side. The menstrual history was normal and the remaining history not significant.

PLATE VI




Case 8-813

*Physical Examination:* The patient was a well-developed, well-nourished girl, whose breath was slightly foul. There were tonsillar remnants and a slight thyroid enlargement; the abdomen was normal, as was the nervous system.

*Laboratory Summary:* The patient was 9 per cent above her predicted weight and showed a basal rate of —14 per cent, with low blood pressure. Alveolar carbon dioxide was normal. The urine was somewhat scanty, but was otherwise normal. Her protein intake was below a maintenance level, the residual nitrogen fraction high. The phthalein output was below normal. Her sugar tolerance was half the normal. The blood uric acid was relatively slightly high. The blood showed a somewhat low hæmoglobin and a slight leucocytosis, with substantially normal leucocytic formula.

*X-Ray Examination* showed some obscuration of all the sinuses.

*Barany Test* gave normal findings.

*Eye Examination* gave a positive Ewing test, with slight enlargement of the blind spots.

*Audiogram* showed a definite loss of hearing in both ears, which were substantially alike.

*Discussion:* The presenting picture here was one of ovarian failure. Ovarian medication was recommended and for a time the patient followed it. The basal rate improved, also the blood pressure. There was no great change in the hearing, although some slight improvement was noted. More recently the patient has shown a return to the earlier level of hearing. She is seriously circumscribed and in anticipation of the future has begun to study lip reading. That she has not followed her medication there can be no doubt, although it is questionable if her patent endocrine defect and her hearing failure have any association. Correction of her pan-sinusitis was also recommended, but this, like her medication, has not been carried out.

CASE S-1690. There are several points of interest in this case, which is one of progressive deafness in a girl of 20. The condition began at the age of 10 and was progressive for a period of about 4 years. During the past 6 years it had remained unchanged so far as the patient could tell. There had been some catarrh during the early years, but this disappeared without any improvement in the hearing. The patient had been given pituitary extract at one time, but without affecting the deafness. The patient was a frail child, but with the establishment of the catamenia at the age of 12 she became more robust and was a healthy young girl at the time of her admission.

*Family History:* Cardio-renal disease and diabetes appeared several times among the immediate relatives.

*Past History:* She reported the minor ailments of childhood, a slight attack of tonsilitis, a partial tonsilectomy at 4 and a tonsil and adenoid operation at 12, and a brief attack of pyelitis at the age of 10. The patient reported a discharging ear early in the period of her deafness. This was, however, of brief duration. The remaining history, including that of the catamenia, was essentially irrelevant.

*Physical Examination* showed a well-developed and well-nourished girl. The speaking voice had the peculiar quality so frequently noticed in the deaf. There was excessive pilosity of arms, legs and spine, but the configuration of the pubic hair was normal. There was some acne on face and chin. The patient was distinctly deaf, but could apprehend loud speech. The blood pressure was low. The remaining findings were normal.

*Laboratory Summary:* The patient was within 1 per cent of her predicted weight. The basal rate was —12 per cent, blood pressure low, carbon dioxide a low normal. The urine and blood findings were normal, except for a slight lymphocytosis. The patient was in college and it was suggested that the tests of sugar tolerance be performed there. The whole general picture of the patient suggested an ovarian failure. Twenty grams of sugar were sent and the test was reported as negative. Later, a 40-gram test was also reported as negative. Sixty grams were sent, but as it was approaching vacation time the patient waited until she returned home to complete the test. In the meantime, examination of the existing data confirmed the earlier opinion of a probable gonad failure, with which the sugar test was wholly at odds. On the return of the patient to this neighborhood the sugar test was repeated with an initial dose of 20 grams, to which the patient gave a positive response. A second 40-gram dose gave a very marked positive response, while the response to 10 grams was negative.

*Nose and Throat Examination:* Tonsillar remnants were noted, but were apparently unoffending. There was a deflected septum, producing partial obstruction.

*Ear Examination* gave normal findings.

*Barany* test indicated normal conditions.

*Audiogram:* Marked uniform loss of hearing in both ears was disclosed.

*Radiography:* The sinuses were all normal. The patient showed one unerupted molar.

*Discussion:* The repeated sugar test completed the picture of a definite primary ovarian failure, and treatment with follicular hormone was recommended. It may well be argued that as the patient's deafness began before the establishment of the catamenia that there could be no connection between her presenting difficulty and her patent endocrine defect. We are wholly unwilling to attempt to establish any artefactural relationship between the two conditions. Recommendation for treatment of the endocrine condition was made solely to normalize the patient's general metabolism. That any betterment to the ear condition could accrue was wholly problematical. It should be said in passing that many of the subjects of deafness studied by us who demonstrate endocrine defects show a deafness which derives from a definite and demonstrably non-endocrine cause. The normalization of the endocrine status of such patients can only influence the hearing defect by indirection, if at all.

TABLE XXII

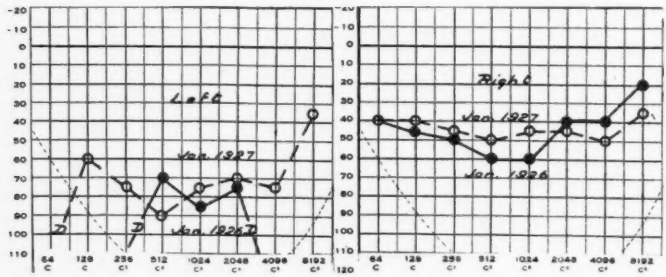
| | Genital Arrest | | Obesity | | Functional Failure | Asoospermia |
|---|---|---|---|---|---|---|
| | | | Castrate | Functional | | |
| Case Number | B-441 | S-952 | B-50 | S-1229 | B-610 | S-1402 |
| Sex | F | M | F | F | F | M |
| Age (yrs.) | 21 | 10 | 51 | 39 | 15 | 27 |
| Height (cm.) | 148 | 146 | 154 | 159.0 | 142.7 | 180.5 |
| Weight (kgm.) | 46.6 | 5.5 | 110.0 | 94.5 | 39.5 | 84.5 |
| Weight Deviation (%) | −2 | +34 | +107 | +65 | +7 | +8 |
| Lung Volume Deviation (%) | −33 | −9 | −58 | −37 | −15 | +2 |
| Basal Rate Deviation (%) | −17 | −1 | −17 | −17 | (+2*) | −3 |
| Blood Pressure (mm.) | 86/58 | 100/65 | 180/94 | 150/88 | 90/44 | 120/70 |
| Pulse Rate (per min.) | 76 | 86 | 56 | 67 | 72 | 72 |
| Temperature (deg. F.) | 97.2 | 99.6 | 97.0 | 97.8 | 98.2 | 97.2 |
| Alveolar $CO_2$ (mm.) | 42 | 38 | 36 | 40 | 36 | 44 |
| Urine Volume (cc.) | 1180 | 1040 | 720 | 720 | 500 | 880 |
| Spec. Grav. | 1.019 | 1.032 | 1.027 | 1.029 | 1.015 | 1.032 |
| Albumin | + | 0 | 0 | 0 | + | 0 |
| Casts | + | 0 | 0 | 0 | 0 | 0 |
| Sugar | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Nitrogen (gms.) | 10.44 | 14.60 | 8.46 | 6.55 | 4.43 | 14.00 |
| Residual Nitrogen (%) | 15.1 | 6.6 | 11.3 | 6.6 | 4.9 | 11.0 |
| Phen. Sulph. Phthal (%) | 62 | 67 | 42 | 52 | 53 | 49 |
| Galac. Tol.— | | | | | | |
| Normal (gms.) | 40 | 30 | 20 | 40 | 40 | |
| Observed (gms.) | 20 | 30 | 20 | 30 | 20 | not done |
| Deviation (%) | −50 | ±0 | ±0 | −33 | −50 | |
| Blood— | | | | | | |
| Non-Protein Nitrogen (mgm.) | 27 | 33 | 33 | 27 | 37 | 29 |
| Uric Acid (mgm.) | 3.0 | 2.9 | 5.3 | 3.0 | 3.7 | 3.7 |
| Sugar (mgm.) | 91 | (118) | (113) | 107 | 93 | 99 |
| Haemoglobin (%) | 100 | 85 | 100 | 70 | 80 | 90 |
| Erythrocytes ($10^6$) | 5.30 | 5.56 | 5.12 | 3.80 | 4.80 | 4.50 |
| Leucocytes ($10^3$) | 10.20 | 13.20 | 7.70 | 9.80 | 6.50 | 9.40 |
| Neutrophiles (%) | 69 | 75 | 32 | 69 | 44 | 71 |
| Lymphocytes (%) | 24 | 20 | 54 | 27 | 44 | 20 |
| Eosinophiles (%) | 1 | 0 | 10 | 1 | 3 | 3 |
| Monocytes (%) | 6 | 5 | 2 | 3 | 9 | 6 |
| Misc. (%) | 0 | 0 | 2 | 0 | 0 | 0 |

GROUP IX. DEVELOPMENT ARREST

CASE B-441. The patient was a 21-year-old girl whose chief complaint was of physical and mental retardation. She was also very deaf in the left ear, less so in the right. The patient was an eight-months baby, and at birth was not expected to live. She showed developmental retardation from birth, being 4 years old before she began to talk. The developmental retardation has been even more marked since her fourteenth year, at which time the period first appeared. Her deafness also dated back to early childhood. There was no paracusis, some tinnitus and no apparent change in her deafness for some years past. The various deficiencies had brought about a shut-in existence, though the patient was not outspokenly asocial.

*Family History:* Twin sisters of the patient died a few hours after birth. There were several other surviving children, all of whom were normal.

PLATE VII




**Case B-441**

*Past History:* The patient reported minor ailments and a tonsil and adenoid operation at 17. The remaining history, including that of the catamenia, is entirely uneventful.

*Physical Examination:* The patient was of small stature and fairly well proportioned, although the chest and hips were relatively somewhat large. There was a marked hair growth on the arms and legs and the heavy pubic hair showed a masculine type of distribution. There was obviously marked mental retardation. Much acne was observed on both face and back. Both ears were deaf, the right less markedly so. Some tonsillar remnants were noted. There was a loud systolic murmur at the cardiac apex transmitted to the axilla, a systolic murmur over the base transmitted to the neck and more pronounced over the aortic area.

*Laboratory Summary:* The patient was less than 5 feet tall; her sitting height index was high, so that she was actually overweight instead of the 2 per cent below prediction which was recorded. The basal rate was —17 per cent, with low blood pressure. Both albumin and casts were reported in the urine and the residual nitrogen was very high. The sugar tolerance was half the normal level.

*Radiography:* The skull was normal.

*Audiogram:* The patient showed a marked loss of hearing in the right ear, and positive hearing in the left was obtainable only at frequencies of 512, 1024, and 2048 (see plate).

*Neurological Examination* disclosed gross change in the 8th nerve and various vegetative disturbances.

*Ear Examination:* The drums were retracted and the cones of light were broken.

*Pelvic* findings were normal, except for the excessive hirsuties.

*Eye* findings were apparently normal.

*Discussion:* The patient presented a picture strongly suggesting ovarian failure. Attention is called in this connection to the high sitting height index, a condition on which comment has already been made. She was placed on ovarian medication (follicular hormone), and one year later was returned to the Clinic for brief study. The height was unchanged, but she had increased 4 kgm. in weight. The basal rate was —9 per cent and the blood pressure 110/60. The lowered sugar tolerance had become normal, 40 grams being necessary to produce a positive response. The audiogram showed a striking improvement (see plate). There was also said to be definite evidence of clinical betterment.

CASE S-952. The patient was a boy of 10 who was referred for obesity, genital arrest, and feminine contour of body. Prior to the time of birth the mother became very toxic and delivery was advised in the seventh month. She carried him to term, however, and was delivered by a high forceps operation. He weighed 9½ pounds at birth, but the genitalia were very small. He did not talk until he was 3 years old. At 4 he had a severe case of whooping cough, followed by bronchial pneumonia. Since then he had had frequent recurrent attacks of bronchitis. The obesity developed after the pneumonia. He had always shown a preference for female companions and was constantly seeking to be kissed by his female relatives, but within the last few months he had begun to play only with boys and had lost his desire to be fondled. He had made an unusually good record in school and had shown unusual musical gifts.

*Family History* was irrelevant.

*Past History:* Only minor ailments of childhood in addition to the record given above were reported. A tonsil and adenoid operation was performed 3 years ago. He had an occasional severe headache. Some years previously "a gland in the middle of the neck became inflamed, but subsided spontaneously." He was constipated when very young.

*Physical Examination:* The boy was an obese lad of 10, with very wide hips, very small genitalia, and large breasts of the feminine type. There was a large pad of fat below the umbilicus. The very small testicles while being examined were retracted into the ring. The boy showed third degree flat-foot and no pilosity.

*Laboratory Summary:* The boy was reported as 34 per cent overweight, with a fairly normal sitting height index. The basal rate was 1 per cent below prediction, blood pressure low, and the pulse somewhat rapid. There was a slightly febrile temperature, and if correction were made for this it would reduce the basal rate deviation to about the low normal level. The sugar tolerance was normal; in fact, all of the other observations were normal, with the exception of a slight leucocytosis.

*Radiography:* The skull was normal.

*Eye Examination:* Normal.

*Discussion:* The picture presented here was similar in kind to that produced by castration. The boy was reported by us as a con-

genital gonad failure. As there was no reason to anticipate betterment from any of the suggesting methods of treatment, no recommendations as to therapy were made. The boy was requested to return in 2 years for a repetition of the study.

### GROUP X. OBESITY

CASE B-50. The patient was an extremely obese woman 51 years of age who had had a pan-hysterectomy 28 years before. She was married 30 years earlier, and in the brief interval of 2 years conceived twice, but each time induced abortion in the second month. A hysterectomy was then performed, although the patient did not know the reason for this operation. She weighed 135 pounds at the time of her marriage. After her operation she began to increase in weight and a year before she was admitted to this Clinic weighed over 260 pounds. She stated that diet was ineffective in weight reduction, but that for 15 years past she had been taking thyroid intermittently, at times reaching 8 grains a day. She stated that under thyroid medication she always lost weight, but became very weak and suffered from palpitation. She had been without medication for some time prior to her admission. She also complained of a throat trouble which began 15 years before and consisted chiefly of a dry, scratchy sensation.

*Family History:* One sister had diabetes. The remaining history was irrelevant.

*Past History:* In addition to the matters detailed above, the patient reported minor ailments, diphtheria, typhoid, influenza, and frequent attacks of pharyngitis. She had had some loss of hearing in the left ear for many years. The teeth were in fair condition. She complained of attacks of hoarseness. The gastro-intestinal history was entirely normal. She denied venereal disease, and we were unable to secure the information on this point that we desired. The Wasserman reaction was negative. She complained of some nocturia. The menses were established at the age of 12 and the history was uneventful up to the time of her operation. She had used alcohol freely throughout her life.

*Physical Examination:* The patient was a very obese woman of 51, the trunk being relatively more obese than the legs. The pupils were sluggish in their reaction to light, but reacted well to accommotion and were equal and regular. The tongue showed no tremor, the teeth were in poor condition, there was no thyroid enlargement, the breasts were very large and pendulous. Coarse, bubbling rales were noted, most marked at the end of expiration and confined to the right side. They were increased by coughing. The blood pressure was very low. The abdomen was normal. The routine neurological findings were normal.

*Laboratory Summary:* The patient was just over 5 feet tall and 107 per cent above her predicted weight. Her sitting height index was substantially normal. There was marked loss in lung volume. The basal rate was —17 per cent, with a somewhat slow pulse and a hypertensive blood pressure. Alveolar carbon dioxide was low. The urine was somewhat scanty, otherwise not remarkable. Residual nitrogen was high; the phthalein output below the normal. The patient gave a positive test with 20 grams of galactose, the level to be predicted from the history of her earlier operation, and negative with 10. There was a high blood uric acid, a marked lymphocytosis, and a 10 per cent œsinophilia.

*Ear Examination:* The drum heads showed a moderate degree of chronic catarrhal thickening. In addition, the examiner found evidence of a low degree of toxæmia affecting the auditory nerve.

*Nose and Throat Examination:* There was a slight septum deviation, somewhat large, cryptic tonsils, and a slight inflammatory condition of the larynx.

*Radiography:* The skull and chest were normal, though the plates of the latter were somewhat unsatisfactory because of the thick chest wall.

*Discussion:* The whole history of this case, coupled with the laboratory examination, suggests an obesity arising from the patient's surgical hypogonadism. There is no suggestion here of thyroid failure which could not equally be referable to the ovarian loss. The œsinophilia and high blood uric acid would carry a suggestion of pituitary involvement, which was, however, denied by certain of the other observations. We were not able to complete the study on this patient and the chest condition, and that of the cardio-vascular system remained largely unevaluated. The patient was recommended to take ovarian medication, but the habit of years determined her to continue with the thyroid. We speedily lost track of her, but one of us learned later that she had become psychotic and had died within a few years of the study at the Boston Psychopathic Hospital. As noted above, complete cooperation could not be secured and the study, of necessity, remained incomplete.

CASE S-1229. This patient was a very obese woman, 39 years of age, who complained of cramp in the upper abdomen. The onset of this condition had been a few days before. She also complained of her obesity, which apparently began in young girlhood. For a number of years she had been increasingly fatigable, and with the onset of the pain element had become nervous and irritable. There was reason to believe that this latter factor was of materially longer duration than the preceding few days.

*Family History:* There were numerous records of cardio-renal and cardio-vascular disease in her immediate family.

*Past History:* She reported the minor ailments of childhood, a tendency to infections of the respiratory tract, and rheumatism. She had had tonsilitis and endocarditis in 1917. She had worn glasses for the last 5 years, and when tired was unable to focus the eyes properly. She had had several attacks of conjunctivitis in the left eye within the past few months. She was troubled with flatulency, but only when nervous and tired. The catamenia was established at the age of 11; the periods were regular at 42-day intervals, the flow was scanty.

*Physical Examination:* The patient was a very obese woman with the fat generally distributed, presenting hypertrichosis on the face, heavy hair growth on the arms and legs, and masculine distribution of heavy pubic hair. The palms of the hands showed a slight eczematous involvement. The majority of the teeth were missing, and those remaining were in only fair condition. The tonsils were hypertrophied and apparently not offending. There was a slight systolic murmur and a slightly high blood pressure. The remaining findings were not remarkable.

*Laboratory Summary:* The patient was 65 per cent above her predicted weight, with normal sitting height index. She was definitely below her predicted lung volume. The basal rate was —17 per cent, the blood pressure somewhat high. The urine was scanty and

concentrated, but otherwise normal. The sugar tolerance was somewhat depressed; blood composition normal, but with some degree of secondary anæmia.

*Eye Examination:* The left upper form field was somewhat cut, due to a drooping eyelid; the remaining findings were normal.

*Discussion:* Only a limited study could be made on this patient and emphasis was laid on the purely endocrine aspects. The picture presented was suggestive of primary ovarian failure, although a pituitary dysfunction was not excluded. Ovarian medication was recommended and we believe has been followed in some measure. Indirect report suggests some but not striking improvement.

### GROUP XI. FUNCTIONAL FAILURE IN EARLY ADOLESCENCE

CASE B-610. This patient was a 15-year-old girl whose presenting difficulty was her small stature, she being but 4 ft. 9 in. tall. From the time of her early childhood she had been smaller than the other girls of her own age.

*Family History* was entirely irrelevant. Three siblings died in infancy of diphtheria, and five surviving brothers and sisters were all normal.

*Past History:* The patient had influenza at the age of 7 and pneumonia a year later. The catamenia was established eight months before, and in this interval the patient had had four periods which were substantially normal. The remaining history was not significant.

*Physical Examination:* The patient was a small, well-developed and well-nourished girl of 15. There was a very slight thyroid enlargement, a few moist rales at the right apex, increased vocal fremitus in the interscapular region; the knee jerks were sluggish. The remaining findings were completely normal.

*Laboratory Summary:* The patient was 7 per cent above her predicted weight, with normal sitting height index. The basal rate as recorded was 2 per cent above prediction. This was incorrect and the test was not entirely satisfactory; the true rate was undoubtedly below this level. A second examination could not be secured. The blood pressure was definitely low, as was the carbon dioxide. The urine was scanty and contained albumin. The protein intake, as indicated by the nitrogen elimination, was below a maintenance level. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The nitrogenous elements of the blood were slightly high. The blood showed a relative lymphocytosis and a 3 per cent eosinophilia.

*Radiography:* The bone development of the knees and shoulders was normal; the sella shows enlarged posterior clinoids.

*Discussion:* This case again could be regarded as one of pituitary dysfunction. The bulk of the evidence, however, was more suggestive of an inadequacy of gonad function. She is reported as improved, but we have had no further contact with her.

CASE S-1402. The following case is particularly interesting in view of certain beliefs that have been generally current during the past few years in relation to bodily vigor, libido and the status of the male gonads.

The patient was a large, powerful man of 27, whose complaint

was of sterility. He had been married for about two years and had had satisfactory intercourse every night since his marriage, with the exception of two or three intervals of 3-4 days each. He had no difficulty in securing an erection, but believed that his ejaculation time was somewhat rapid, as he would have his orgasm within twelve or fifteen strokes after immission. His deduction is not necessarily correct, as both he and his wife always have orgasm. In 1917, ten years previously, he had had the mumps with orchitis as a complication. Several examinations since marriage had shown a complete absence of spermatozoa from the semen.

*Family History* showed one case of cancer, but was otherwise irrelevant.

*Past History:* In addition to the mumps he reported the minor ailments of childhood, scarlet fever, influenza at the time of the epidemic, and recurrent sore-throats in childhood, with one quinsy. He had headaches as a boy; none for several years, however. The remaining history was entirely normal. The patient was the driver of a truck, handling groceries in bulk, such as barrels of sugar and large cases of canned goods. He worked from 3 a. m. to noon, and acknowledged that "at times he felt tired at the end of the day's work." Three years previously he had strained his side in lifting a barrel of sugar, but examination showed it to be no more than this, and he had had but little subsequent trouble from it.

*Physical Examination* showed a very well developed, muscular young man. The nose showed some obstruction and the presence of a serous discharge (the patient had a head cold); the teeth were in fair condition only; the tonsils were somewhat hypertrophied. A few moist rales were noted at the right apex. Body hair was normal in amount and distribution. The testicles were less than half the normal size and there was a small left varicocele. The remaining findings were normal.

*Laboratory Summary:* The patient was nearly six feet tall; he was 8 per cent overweight and slightly above his predicted lung volume. The basal rate was entirely normal, as were the complementary measurements. Only the temperature was slightly low. The urine had a slightly low volume, but elimination was fair. The residual nitrogen fraction was high; the remaining findings normal. The blood cells showed a predominance of neutrophiles and a 3 per cent eosinophilia. The blood uric acid was relatively high, the serological findings were normal.

*Laryngological Examination:* The tonsils were found to be definitely infected.

*Cystoscopy* showed a small degree of posterior urethritis.

*Eye Examination:* The blind spots were slightly enlarged.

*Genito-urinary Examination:* The two lobes of the prostate were slightly enlarged and boggy. Several condom specimens showed complete azoospermia.

*Neurological* findings were normal.

*Discussion:* We regard this case as peculiarly informative. The patient is a young man with markedly atrophied testes and seemingly a complete loss of spermatogenic function. Physically he is vigorous, hardy and strong beyond the average. Sexually, his libido and his power to have intercourse, satisfactory to himself and his partner, is distinctly above the average. Diagnoses of hypergenitalism

**have been made on a less enduring performance than is his, and yet there is a demonstrable gonad failure so far as the exocrine function is concerned. We do not attempt to explain it. We only offer the facts.**

Review of the preceding protocols demonstrates one striking difference between the cases presented and those recorded in the earlier thyroid and pituitary papers. A number of them derived from a mutilating operation with complete removal of the endocrine organs. For these, naturally, no effective treatment was available. Some of the others resulting from functional failure were placed under endocrine medication and responded favorably. In many instances, however, recourse to endocrine therapy was seemingly ineffective. This outcome must be regarded as the result of several factors. In the first place, review of the individual case protocols will disclose a record of many incomplete studies, left so because of the incooperation of the patient. Comment has been made in the body of the paper on the personality change frequently associated with ovarian failure. This has operated not only to lessen the thoroughness of the particular individual studies but also has hindered a faithful performance of the therapeutic program suggested. A second factor is found in the inadequacy of the medication. Many ovarian preparations apparently are relatively inert and the huge dosage which would be necessary to secure adequate response is but seldom offered. As already noted in the pituitary paper, one prime factor in the frequent statement that anterior lobe medication is ineffective rests upon the failure of the physician in charge of the case to prescribe an adequate dosage. As recorded in the earlier paper, one of the patients in the pituitary series showed definite improvement only with a level of medication of 104 grains of anterior lobe material daily. Many others seemingly required a daily intake of from 50 to 75 grains to restore them to a normal functional level. Thanks to the brilliant work of several investigators, among whom Doisy and Allen (57) should not fail of mention, more active ovarian material is now available for clinical use. Results obtained with this are far more encouraging and productive in our experience than was usually the case with the earlier preparations. The subject is a large one and equally one of great importance. It is planned by one of us (C. H. L.) to present in the near future a much more extended analysis of the results

of ovarian therapy than could suitably find place in this article. It is permissible, however, to say that in the more recent cases in which ovarian therapy has been indicated by the establishment of a diagnosis of primary ovarian failure, the results are far more encouraging and hopeful than was formerly the case. While these materials have not been available for a sufficiently long time to allow for such thorough studies of the results of medication as are available for the pituitary and the thyroid investigations, the trends of betterment disclosed warrant the same degree of confidence in the validity of diagnoses as are given by the results of therapeutic testing in pituitary and thyroid disorders.

The cases in the foregoing section were selected to illustrate some given point as strikingly as possible. Many of the other cases in the series presented uncomplicated functional failures, and a large part of these have responded satisfactorily to treatment. As cases, they are lacking, however, in the distinctive special features of those selected for this series of protocols and their consideration belongs more properly to the forthcoming paper which will be devoted primarily to a discussion of the results of treatment.

The authors wish to express their sincere and grateful thanks to the colleagues and associates who as members of the staff have contributed so much to their studies, to their other colleagues from whose reference have derived many of the interesting and significant cases in the series and finally to the patients themselves for their cooperation in the work.

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# STUDIES OF OXYTOCIN AND VASOPRESSIN: THE EFFECT ON FROG MELANOPHORES

L. W. ROWE, M.S.
Medical Research Laboratories, Parke, Davis & Co.
DETROIT

The effect of pituitary posterior lobe extracts upon the pigment system of Amphibia has been the subject of careful investigation by groups of English workers, particularly Hogben and Winton (1 and 2). These authors reported upon the specificity of potent pituitary extracts as melanophore stimulants, using frogs (Rana temporaria) as test animals. The earlier work of Spaeth (3) on fish, and Swingle (4) and McCord (5) on tadpoles, was also considered. They decided that the melanophore stimulant is probably identical with the oxytocic principle, and that this test could be used as a quantitative means of assay for pituitary extracts (2).

Other workers—Dreyer and Clark (6), Schlapp (7), and Fenn (8)—reported later that the melanophore stimulant and the pressor principle are probably identical, thus opposing the views held by Hogben and Winton. Since the definite separation of two active principles from pituitary extracts by Kamm, Aldrich, Grote, Rowe and Bugbee (9), it seemed desirable to subject these separated principles to tests on frog melanophores to determine whether this action could be ascribed to either or to both of them.* The value of this melanophore stimulant method as a quantitative means of assay for one or the other of these principles, and the mechanism of the action on the melanophores, seemed also worthy of investigation.

Accordingly, experiments were begun, using frogs (R. pipiens) as the test animals, without decerebration but after "bleaching" in bright light on a white background. Injections were all 0.5 cc. in volume, and made intraperitoneally into medium sized frogs, room temperature (about 25° C.) being used. A series usually consisted of 4 frogs of about the same weight,

*In a personal communication to Dr. Kamm, Prof. C. G. MacArthur, of the University of Buffalo, reports that the pressor principle is responsible for melanophore stimulation.

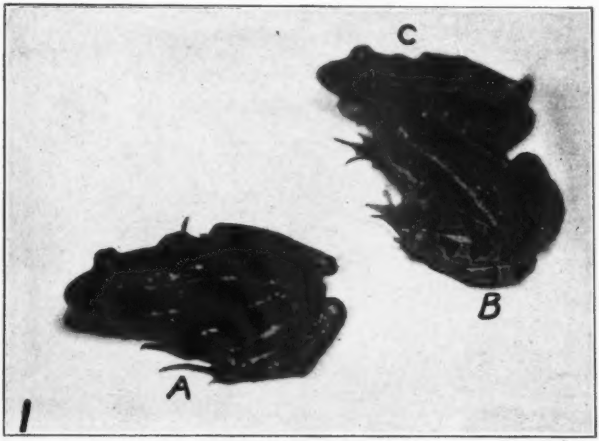
one of which received a dilution of the oxytocic principle (Oxytocin) equivalent to standard U. S. P. X pituitary extract; another a dilution of the pressor principle (Vasopressin), equivalent to standard surgical Pituitrin in pressor potency; another, a dilution of standard surgical pituitary extract (Pituitrin, S), and the fourth served as a control. The control frog was frequently not injected at all, but sometimes was injected with salt solution and sometimes with distilled water. Some twenty series were injected and the results in each series may be briefly detailed as follows:

| Series | Frog Wt. | Dose | Melanophore Effect |
|---|---|---|---|
| 1 | 10 gms. | Vasopressin, 1-2000 | Expanded. Visibly dark +++ |
| 1 | 12 gms. | Oxytocin, 1-1000 | Very slightly visible, + |
| 1 | 10 gms. | Pituitrin "S," 1-2000 | Very slightly visible, + |
| 2 | 13 gms. | Oxytocin, 1-1000 | No visible effect, O |
| 2 | 12 gms. | Pituitrin "S," 1-2000 | Slightly visible, ++ |
| 2 | 12 gms. | Vasopressin, 1-2000 | Very slightly visible, + |
| 3 | 14 gms. | Pituitrin "S," 1-1000 | Very dark ¼ to 1½ hrs., ++++ |
| 3 | 13 gms. | Oxytocin, 1-500 | No visible effect, O |
| 3 | 13 gms. | Vasopressin, 1-1000 | Dark ¼ to 1½ hrs., +++ |
| 3 | 12 gms. | Ringers Sol. | No visible effect, O |
| 4 | 13 gms. | Pituitrin "S," 1-1000 | Very dark in ½ hr., +++ |
| 4 | 14 gms. | Vasopressin, 1-1000 | Quite dark in ½ hr., +++ |
| 4 | 17 gms. | Oxytocin, 1-200 | No visible effect, O |
| 5 | 14 gms. | Oxytocin, 1-200 | No visible effect, O |
| 5 | 14 gms. | Vasopressin, 1-1500 | Very slight, + |
| 5 | 18 gms. | Pituitrin "S," 1-1500 | Dark when dosed, became darker |
| 6 | 12 gms. | Pituitrin "S," 1-1000 | Very dark, ++++ |
| 6 | 14 gms. | Oxytocin, 1-50 | Very slight +. Prostrated in 2 hrs. |
| 6 | 16 gms. | Vasopressin, 1-1000 | Dark, +++ |
| 7 | 15 gms. | Oxytocin, 1-100 | No visible effect, O |
| 7 | 16 gms. | Pituitrin "S," 1-1500 | Very dark ¼ to 1 hr., ++++ |
| 7 | 15 gms. | Vasopressin, 1-1500 | Dark ¼ to 1 hr., +++ |
| 8 | 14 gms. | Oxytocin, 1-100 | No visible effect, O |
| 8 | 15 gms. | Vasopressin, 1-2000 | Fairly dark, ++ |
| 8 | 15 gms. | Pituitrin "S," 1-2000 | Dark, +++ |
| 8 | 14 gms. | Distilled water | No visible effect, O |
| 9 | 16 gms. | Vasopressin, 1-1000 | Dark ¼ hr. to 1 hr., +++ |
| 9 | 17 gms. | Pituitrin "S," 1-1000 | Very dark ¼ to 1 hr., ++++ |
| 9 | 18 gms. | Oxytocin, 1-100 | Light, O |
| 10 | 18 gms. | Oxytocin, 1-100 | Light, O |
| 10 | 16 gms. | Pituitrin "S," 1-1500 | Very dark ½ to 1½ hrs., ++++ |
| 10 | 19 gms. | Vasopressin, 1-1500 | Dark ½ to 1½ hrs., +++ |
| 11 | 20 gms. | Oxytocin, 1-100 | Light, O |
| 11 | 18 gms. | Vasopressin, 1-1000 | Dark, +++ |
| 11 | 18 gms. | Pituitrin "S," 1-1000 | Very dark, ++++ |
| 12 | 12 gms. | Pituitrin "S," 1-2000 | Dark in ½ hr., +++ |
| 12 | 12 gms. | Oxytocin 1-100 | Dark in ½ hr., +++ |
| 12 | 12 gms. | Vasopressin, 1-2000 | Dark in ½ hr., +++ |
| 13 | 20 gms. | Pituitrin "S," 1-1000 | Very dark in ¼ to 1 hr., ++++ |
| 13 | 20 gms. | Oxytocin, 1-50 | Light all the time, O |
| 13 | 20 gms. | Vasopressin, 1-1000 | Dark in ½ hr. to 1 hr., +++ |
| 14 | 19 gms. | Oxytocin, 1-100 | Slightly dark, + |
| 14 | 20 gms. | Pituitrin "S," 1-1000 | Fairly dark, ++ |
| 14 | 18 gms. | Vasopressin, 1-1000 | Fairly dark, ++ |
| 15 | 14 gms. | Vasopressin, 1-2000 | Dark in ¼ to 1 hr., +++ |
| 15 | 14 gms. | Oxytocin, 1-100 | Light all the time, O |
| 15 | 14 gms. | Pituitrin "S," 1-2000 | Very dark, ++++ |
| 16 | 15 gms. | Vasopressin, 1-2000 | Medium to light, ++ |
| 16 | 16 gms. | Oxytocin, 1-100 | Light all the time, O |
| 16 | 14 gms. | Pituitrin "S," 1-2000 | Dark, +++ |
| 17 | 18 gms. | Vasopressin, 1-3000 | Dark in ¼ to 1 hr., +++ |
| 17 | 18 gms. | Oxytocin, 1-100 | Light all the time, O |
| 17 | 18 gms. | Pituitrin "S," 1-3000 | Very dark ¼ to 1 hr., ++++ |
| 18 | 17 gms. | Vasopressin, 1-4000 | Dark ½ to 1 hr., +++ |
| 18 | 16 gms. | Oxytocin, 1-100 | Lighter than when dosed, O |
| 18 | 18 gms. | Pituitrin "S," 1-4000 | Dark ½ to 1 hr., ++++ |

| Series | Frog Wt. | Dose | Melanophore Effect |
|---|---|---|---|
| 19 | 12 gms. | Vasopressin, 1-4000 | Fair, ++ |
| 19 | 12 gms. | Pituitrin "S," 1-4000 | Dark, +++ |
| 19 | 16 gms. | Oxytocin, 1-500 | Light all the time, O |
| 19 | 20 gms. | Pituitrin "S," 1-5000 | Fair, ++ |
| | | 20th Series. Carefully decerebrated | |
| | 15 gms. | Pituitrin "S," 1-4000 | Very dark, ++++ |
| | 12 gms. | Vasopressin, 1-4000 | Dark, +++ |
| | 12 gms. | Oxytocin, 1-100 | Light, O |
| | | 21st Series. Carefully Decerebrated | |
| | 10 gms. | Vasopressin, 1-5000 | Fair, ++ |
| | 10 gms. | Pituitrin "S," 1-6000 | Dark, +++ |
| | 10 gms. | Oxytocin, 1-50 | Very dark (later lighter), ++++ |
| | 15 gms. | Distilled water | Slight, + |
| | | 22nd Series. Carefully Decerebrated | |
| | 15 gms. | Vasopressin, 1-8000 | Fair, ++ |
| | 15 gms. | Pituitrin "S," 1-10,000 | Fair, ++ |
| | 15 gms. | Oxytocin, 1-80 | Fair, ++ |
| | 15 gms. | Control, not dosed | Slight, + |
| | | Isolated Skin Tests | |
| | Strip of web | Vasopressin, 1-4000 | Fair, ++ |
| | Strip of web | Oxytocin, 1-100 | Slight, +? |
| | Strip of web | Pituitrin "S," 1-4000 | Contracted ? |
| | Strip of web | Vasopressin, 1-1000 | Good, ++++ |
| | Strip of web | Oxytocin, 1-50 | Some, + |
| | Strip of web | Pituitrin "S," 1-1000 | Good, ++++ |

## DISCUSSION

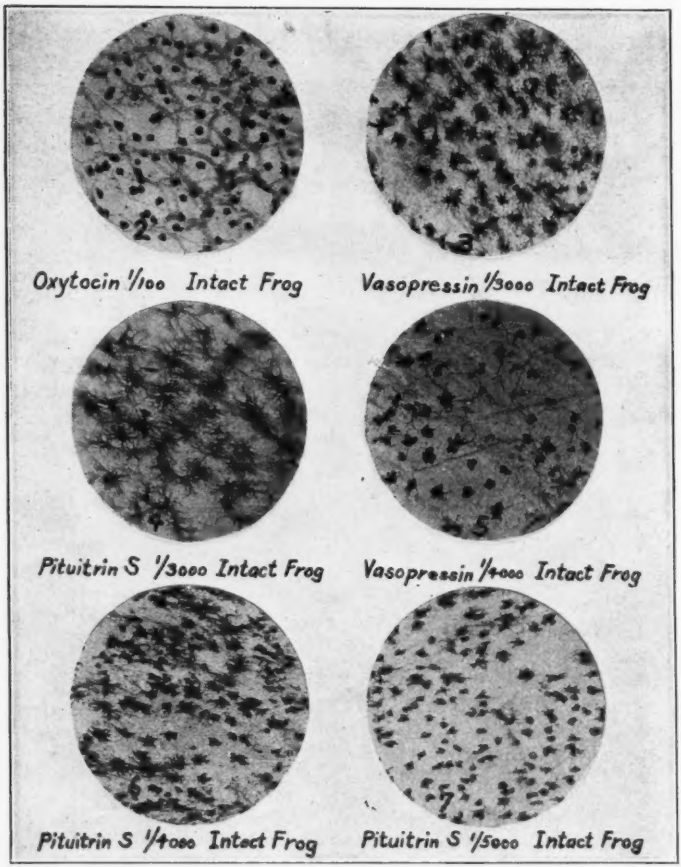
In considering roughly the results detailed above, it can be seen that melanophores of the intact frog (R. pipiens) are quite sensitive to pituitary extract (Pituitrin) and to its pressor principle (Vasopressin). The melanophores are not appreciably ex-



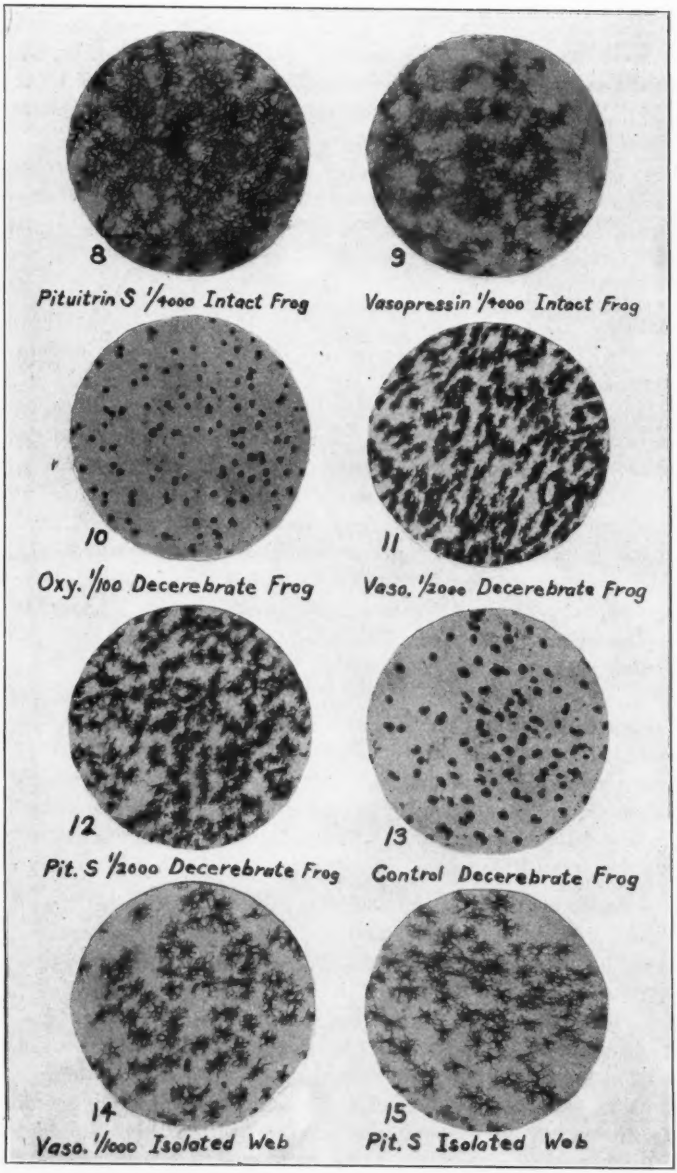

A=Pituitrin "S," 1/3000. B=Oxytocin, 1/100. C=Vasopressin, 1/3000.

panded by relatively large doses of the oxytocic principle (Oxytocin). These facts are apparent from macroscopic observation of the intact animals, and the photograph (No. 1) illustrates this.

Most of the experiments were made with intact animals, rather than by following the technique of Hogben and Winton (1) because it seemed desirable to simplify the test, if possible, in order to put it on a practical basis; and also it was quickly


Oxytocin 1/100 Intact Frog
Vasopressin 1/3000 Intact Frog
Pituitrin S 1/3000 Intact Frog
Vasopressin 1/4000 Intact Frog
Pituitrin S 1/4000 Intact Frog
Pituitrin S 1/5000 Intact Frog

observed that the intact animals were very sensitive, though not as sensitive as the decerebrated animals. The results with the intact animals were sufficiently erratic to indicate that it would not be a suitable method for quantitative control of pressor


8
Pituitrin S 1/4000 Intact Frog
9
Vasopressin 1/4000 Intact Frog
10
Oxy. 1/100 Decerebrate Frog
11
Vaso. 1/2000 Decerebrate Frog
12
Pit. S 1/2000 Decerebrate Frog
13
Control Decerebrate Frog
14
Vaso. 1/1000 Isolated Web
15
Pit. S Isolated Web

activity, even if the pressor and melanophore principles are actually identical. This is contrary to the quantitative accuracy reported by Hogben and Winton (2) and confirmed by Treuter (10). Kochmann and Wagner (11), however, find the method not more than roughly quantitative.

The tests on the decerebrated animals show them to be more sensitive and probably more accurate, but the quantitative pressor test of Hamilton (12) is much more logical and fully as accurate as a means of assay for the pressor principle.

Grossly, it can also be seen from results on the intact and decerebrated animals that the pressor principle alone (Vasopressin) is appreciably less powerful as a melanophore stimulant than is a pituitary extract of the same pressor potency (Pituitrin, S). The difference in favor of the pituitary extract seems to be about 20 to 25 per cent. This fact is very difficult to explain, if we assume that there are only two active principles in the activity of the posterior lobe. About the only explanation would be the possible divergence due to the sum of the known experimental errors of the pressor and melanophore methods. In that case, there would actually be the difference in *pressor activity* between the Vasopressin and Pituitrin which is apparent by the melanophore tests. This explanation is made rather untenable, however, by the fact that in my experiments several different lots of Vasopressin and Pituitrin S were used, and the pressor experimental error could not always have diverged. The more logical explanation seems to lie in the possibility of a third active principle which is more closely associated with the pressor principle, and consequently has only been partially separated from it in our Vasopressin. This, of course, is only a theory which has not been proved or disproved at this time.

As visible proof of the powerful effect of dilute solutions of Pituitrin and Vasopressin, and the lack of effect of Oxytocin upon the melanophores, the following photomicrographs are presented. A piece of the web of the foot was removed, usually 30 minutes after injection, when the effect was at its height, fixed in formalin and mounted on a microscopic slide. This proved much more satisfactory than fixing skin from the back in Bouin's fluid, as was done by Hogben. These photomicrographs speak for themselves in showing the lack of melanophore stimulant

activity of Oxytocin in 1-100 dilution, but some action in 1 to 50 dilution. They also show the appreciable difference between Vasopressin and Pituitrin, S, though these products have approximately the same pressor activity.

The question of the mode of action of pituitary extracts upon the melanophores has been carefully considered by Hogben and Winton (1). They showed that since pituitary extract acts upon melanophores of isolated frog skin, and since it acts upon melanophores after paralysis of the nerve endings, the action must be a direct one upon the pigment cell itself. This mode of action of Vasopressin has been confirmed to the extent that it acts upon isolated strips of web from the foot of the frog, as shown by the few experiments conducted and the photomicrographs of stimulant action from 1-1000 Vasopressin and Pituitrin, but little action even from a 1-50 dilution of Oxytocin. It would certainly seem that the stimulant action is a specific and direct one upon the cell itself.

## CONCLUSIONS

1. Oxytocin, a solution of the oxytocic principle equivalent to U. S. P. X standard pituitary extract in uterine stimulating activity, does not stimulate frog melanophores.

2. Vasopressin, a solution of the pressor principle, does stimulate frog melanophores, but apparently to an appreciable degree less than a pituitary extract of the same pressor potency.

3. The melanophore stimulant present in pituitary extract may be a separate principle which is more closely associated with the pressor than with the oxytocic principle.

4. The melanophore method is erratic and less sensitive when intact frogs are used, and would not be a suitable bioassay control method for the *pressor* activity of pituitary extract.

5. The mode of action of the melanophore stimulant is apparently a direct one upon the cell itself.

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# RECENT PROGRESS IN THE INVESTIGATION OF THE POSTERIOR LOBE OF THE PITUITARY GLAND*

EDWIN P. BUGBEE, M.D., AND OLIVER KAMM, PH.D.

From the Research Laboratories of Parke, Davis and Company

DETROIT

It is our purpose in the following paper to present a short summary of the experimental work which has recently been done with the posterior lobe of the pituitary gland. This lobe contains two important active principles—an oxytocic principle which causes contractions of the uterus and a pressor principle which raises blood pressure. These two principles have been separated and obtained in a nearly pure form by Dr. Oliver Kamm, Dr. T. B. Aldrich, Dr. I. W. Grote, Mr. L. W. Rowe and Dr. E. P. Bugbee. The oxytocic principle has been named Alpha-hypophamine and our solution containing this active substance, Oxytocin. The pressor principle has been named Beta-hypophamine and our solution containing the substance, Vasopressin. The details of the chemical work involved in the separation of the active principles have been published (1), so we will refer to them only briefly.

Fresh beef pituitaries are carefully dissected so as to separate sharply the posterior from the anterior lobes. The posterior lobes are then desiccated with acetone and extracted with dilute (¼ per cent) acetic acid as in the method originally described by Aldrich (2) and which is now a part of the U.S.P. method. Low molecular weight impurities are removed by salting-out with either sodium chloride or ammonium sulphate and the active principles are thus obtained with the protein fraction. The most of the inert proteins are subsequently removed by means of *anhydrous* acetic acid.

Up to this stage there is accomplished only a concentration of the principles and not a separation from each other. However, after 95 per cent of the foreign proteins have been removed, then the two principles begin to submit to a separation. The

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precipitants used are the organic solvents, acetone, sulphuric ether, and petroleum ether, none of which injure the physiologically active substances.

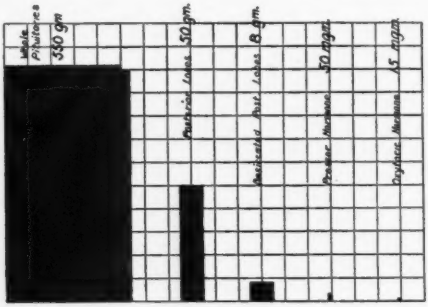
The two hormones, although so very unlike in their physiological behavior, resemble each other not only in chemical nature but also in many of their physical properties, and it is therefore not surprising that as many as twenty fractionations must be conducted in order to secure a satisfactory separation. This is illustrated by the results shown in Table I.

TABLE I

Separation of Oxytocic from Pressor Fraction

| | Ratio of Pressor to Oxytocic Activity |
|---|---|
| Second Fractionation | 100 : 60 |
| Third Fractionation | 100 : 24 |
| Fourth Fractionation | 100 : 14 |
| Fifth Fractionation | 100 : 12 |
| Sixth Fractionation | 100 : 10 |
| Seventh Fractionation | 100 : 8.5 |

Following such an exhaustive fractionation the separate fractions may be recombined, dissolved in acidified water, and diluted back to the original volume, yielding a solution that is




Pituitary Glands from 200 Steers

FIGURE 1

indistinguishable from the original gland extract, thus showing that in the process none of the activity has been injured or one product converted into another.

Figure I shows graphically the relative amounts of pituitary glands and active principles obtained.

Two hundred beef pituitaries weigh 550 grams. The posterior lobes alone weight 50 grams. When desiccated, the posterior lobes weigh only 8 grams. The purified pressor fraction weighs only 0.050 gram and the oxytocic fraction weighs only 0.015 gram. Work is in progress aiming to obtain them in a condition of absolute purity.

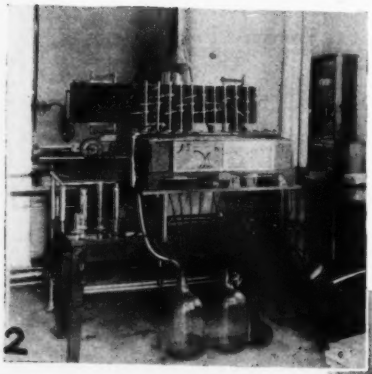
Figure 2 shows the apparatus used for testing the oxytocic activity of a solution. A strip of uterine muscle from a guinea-pig is attached to a writing lever in such a way that its contractions are recorded on the smoked paper of the kymograph. Standard Pituitrin solution is used alternately with the unknown solution until doses of each are found which will cause equal contractions of the uterine muscle. Since the strength of one solution is known, the other can then be computed. The method is prescribed in the Pharmacopoeia of the United States X, page 220, and was originally suggested by Dale and Laidlaw in 1912 (3). The apparatus (4) shown in the photograph consists of an electrically heated water bath containing twelve units, so that twelve muscles can be used simultaneously.

Figure 3 shows a similar apparatus in which six muscles can be tested at the same time.

Figure 4 shows the apparatus and method of determining the pressor activity of pituitary solutions. Dogs are deeply anesthetized with chloretone, and then the carotid arteries are cannulated and connected to mercury manometers, which record on smoked paper. Doses of Standard Pituitrin are injected into the saphenous veins and then doses of the unknown solution are similarly injected. The dosages are varied until equal rises in blood pressure are obtained with Standard solution and unknown solution. Since the potency of one solution is known, the potency of the other can then be computed.

The technical details of the method used in this laboratory may be found in previous publications (1, 5, 6, 7).

An interesting pharmacological action of Pituitrin is the darkening of the skin of frogs and tadpoles. When a frog is exposed to bright sunlight, it becomes very much lighter in color. Then if the frog is injected with Pituitrin it turns almost black within a few minutes. Our colleague, Mr. L. W. Rowe, has demonstrated that Vasopressin produces the color change, while Oxytocin has very little effect.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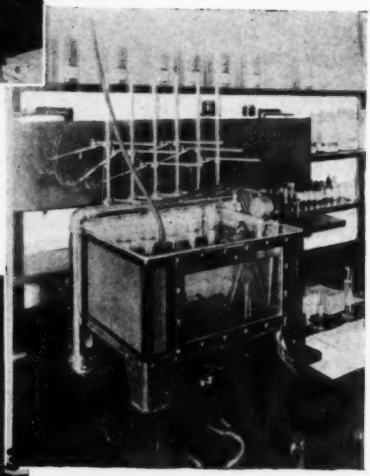

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The pictures illustrating this effect on the skin of the frog are omitted from this paper, as they are shown in another article in this journal (8).

It is well known that pituitary solution has a diuretic-antidiuretic action. By experiments on rabbits we have determined that it is the pressor principle that has this activity (9). In making the tests we used rabbits under urethane, amytal, chloretone or chloral hydrate anesthesia. Cannulas were tied into the urinary bladders and then the number of drops of urine excreted in each 5-minute interval was counted.

Figure 5 shows the results of a typical experiment with a rabbit under urethane anesthesia. In the half hour control period the urine flowed at the rate of 2-7 drops every 5 minutes.

When 0.2 unit of Pituitrin was injected there was first a short latent period or possibly a short period of suppression of urine followed by an increased excretion of urine amounting to 21 drops in 5 minutes. Then followed the antidiuretic effect so that in 40 minutes only 3 drops of urine were excreted.

When 0.2 unit of Vasopressin was injected there was a flow of urine amounting to 25 drops in 5 minutes. This was followed by the antidiuretic effect. No urine was excreted in two 5-minute periods. The antidiuretic effect was subsiding when 0.2 unit of Oxytocin was injected. This was followed by slight increase of flow of urine which may have been due to a small amount of Vasopressin in the solution—about 0.01 unit.

The injection of 0.2 unit of Pituitrin caused a gush of urine which reached the rate of 38 drops in 5 minutes and lasted for 20 minutes. The antidiuretic effect was not apparent after this injection.

The injection of 0.2 unit of Oxytocin produced very little effect.

The injection of 0.2 unit of Vasopressin on the other hand caused diuresis amounting to 29 drops in 5 minutes. This diuresis subsided so that in the course of 35 minutes the antidiuresis began to be apparent.

An injection of 0.2 unit of Pituitrin caused a gush of urine, 28 drops being excreted in 5 minutes. The antidiuretic effect appeared in 25 minutes.

Figure 6 shows another experiment similar to the first. Attention is called to the antidiuretic effect, which is apparently the first effect of injections of Vasopressin and extract of desiccated pituitaries. This early effect has been ascribed to spasm of the ureters.

Figure 7 shows the very slight effect from the injection of 0.1 unit of Oxytocin. The injection of 0.1 unit of Vasopressin, however, is followed by a considerable flow of urine, 73 drops in 5 minutes. This flow subsided in the course of 1 hour, and very little urine was excreted for the next hour.

5 Excretion of Urine by Rabbit Under Urethane Anesthesia




6 Excretion of Urine by Rabbit Under Urethane Anesthesia




8 Excretion of Urine by Rabbit Under Urethane Anesthesia




7 Excretion of Urine by Rabbit Under Urethane Anesthesia




9 Antidiuretic Action of Vasopressin on Normal Man


c.c. Fluid
No Treatment
Vasopressin .25cc. Intram. Every 6 hrs.
No Treatment
Oxytocin .25cc Intram. Every 6 hrs.
No Treatment
Vasopressin .25cc. Nasal Swab Ex. 6 hrs.
No Treatment
Vasopressin .25cc. Intram. Every 4 hrs.
No Treatment
Pituitrin S .5cc. Nasal Swab Ex. 6 hrs.

10 Diabetes Insipidus Patient w/ Pos. Comp. Gilligan and Blumgart

Figure 8 shows quite definitely the *lack* of diuretic-antidiuretic action of even 0.8 unit of Oxytocin. The injection of 0.4 and 0.8 unit of Vasopressin is followed by an immediate antidiuretic effect, followed by a diuretic effect. Probably a subsequent antidiuretic effect would have been observed if the experiment had continued longer.

In normal animals, not under anesthesia, the predominating effect of pituitary extract is the suppression of the flow of urine. This antidiuretic effect, on normal men, has been reported by Gargle, Gilligan and Blumgart (10), who found Vasopressin to have this activity, while Oxytocin had little effect. The antidiuretic action of Vasopressin on normal men has been confirmed by Kamm in our laboratory.

Figure 9 shows the results of a typical experiment. The subject drank 1,000 cc. of water at 7 o'clock in the morning and collected urine at hourly intervals throughout the day.

In the day in which no treatment was given the total urine excreted is shown by the upper line.

On the next day 0.1 cc., or 1 unit, of Oxytocin was given by subcutaneous injection about the same time that the water was drunk. Very little, if any, effect on the urinary excretion was caused by the Oxytocin.

On a subsequent day 0.25 cc., or 5 units, of Vasopressin was given by subcutaneous injection when the water was ingested. The excretion of urine was greatly delayed and even in 12 hours only about one-half of the water had been eliminated.

On another day 0.05 cc., or 1 unit, of Vasopressin was injected about the time the water was drunk. This very small dose had almost as much antiduretic effect as did the dose 5 times as great. An intermediate dose of 3 units of Vasopressin produced an intermediate effect, not shown on the chart.

Gargle, Gilligan and Blumgart (10) have shown that Vasopressin produces the full beneficial effect of Pituitrin when administered to diabetes insipidus patients. Oxytocin was found to be devoid of this effect.

Figure 10 shows the results of the treatment. The dark areas show the amount of water ingested in 24 hours, and the shaded areas show the amount of water eliminated in the same period.

In the day without treatment the patient drank over 8000 cc. of water and passed about the same amount of urine.

On the next day 0.25 cc. of Vasopressin was given by intramuscular injection every 6 hours. The water intake was cut down to 3600 cc. and the output to a nearly equal amount.

On the next day in which no treatment was given, the water intake increased to 5600 cc. and the output was 5500 cc.

On the following day 0.25 cc. of Oxytocin was injected intramuscularly every 6 hours without any effect on the water metabolism.

A day without treatment shows about the same water intake.

On the next day when 0.25 cc. of Vasopressin was given every 6 hours by nasal application, by means of a cotton pledget, there was a great decrease in the amount of water taken in and excreted.

A day without treatment resulted in large intake of water.

Vasopressin, 0.25 cc., given intramuscularly every 4 hours again cut down the amount of water.

Pituitrin S was applied in 0.5 cc. doses intranasally by cotton pledget every 6 hours and also greatly reduced the water intake and output.

These experiments indicate clearly that Vasopressin contains the antidiuretic substance and can take the place of Pituitrin in the treatment of diabetes insipidus patients. An interesting feature of the experiments is the demonstration that intranasal application is more effective than intramuscular injections. This advantage is probably derived from the slower and prolonged absorption obtained in the intranasal administration.

Another action of Vasopressin was noted by Gargle, Gilligan and Blumgart (10) in a patient who was given an intramuscular injection of 0.5 cc. of Vasopressin. There were abdominal cramps, nausea, and diarrhea, thus indicating a stimulating effect on the gastro-intestinal musculature. This same gastro-intestinal effect has been noted by Dr. A. M. Hjort of Dartmouth College. Other investigators have given conflicting reports regarding the stimulation of the gastro-intestinal tract. Further experiments must be performed to settle the matter whether Vasopressin alone has this activity or whether Oxytocin also stimulates peristalsis, but to a lesser degree.

Vasopressin has been used by physicians in several large clinics for the treatment of diabetes insipidus, post operative shock, and the low blood pressure of Addison's disease and brain tumor, with considerable satisfaction.

Oxytocin has also been tested in some of the largest hospitals and found to cause contractions of the uterus in such a satisfactory degree that it may be used in place of Pituitrin in obstetrical practice.

SUMMARY

The posterior lobe of the pituitary gland contains two active principles; an oxytocic principle, which causes contractions of the uterus, and a pressor principle, which raises blood pressure.

These two active principles have been separated and obtained in the form of white, stable, water soluble powders of great potency.

Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place.

The oxytocic principle, which has been named Alpha-hypophamine, causes contraction of uterine muscle when injected into the normal animal, and contracts isolated uterine muscle when applied by contact. It is nearly free from action on other forms of smooth muscle.

The pressor principle, which has been named Beta-hypophamine, does not affect uterine muscle, but stimulates other smooth muscles. It raises blood pressure and stimulates peristalsis in the gastro-intestinal tract. It has both a diuretic and antidiuretic effect. It causes expansion of the melanophores in the skin of frogs.

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# PRONOUNCED EXOPHTHALMOS IN A CASE OF ADENOMATOUS GOITRE WITHOUT HYPERPLASIA

DOROTHY ATKINSON, M. D., H. LISSER, M. D., AND H. CLARE SHEPARDSON, M. D.

From the Ductless Gland Clinic
University of California Medical School
SAN FRANCISCO

Not all are agreed as to whether there is any vital difference between the thyrotoxicosis associated with an adenomatous goitre, and the hyperthyroidism of Graves' disease (exophthalmic goitre). But most authorities are willing to concede that there is a clear differentiation possible between the clinical features of these two types of goitre. It is beside the point, in this communication, to enter into any lengthy discussion of this controversy. Suffice it to state that "adenomatous goitre with hyperthyroidism" (Plummer's disease) is clinically characterized by an asymmetrical nodular enlargement of the thyroid gland in which a thrill is not palpable, and a bruit is not audible, and in which exophthalmos and the so-called thyroid eye signs (VonGraefe, Moebius, Dalrymple, Joffroy, Stellwag) are absent. Graves' disease (exophthalmic goitre), on the other hand, is typified by a symmetrical smooth, highly vascular hyperplastic gland in which a thrill is palpable and bruit audible, and in which exophthalmos and the eye signs referred to above, are present. Both syndromes include nervousness, a subjective feeling of warmth, increased perspiration, palpitation, dyspnoea, tachycardia, tremor, loss of weight and an elevated basal metabolic rate.

Exophthalmos associated with hyperplasia of the thyroid gland needs no discussion as to its frequency, but the following case is considered worthy of record because of the unusual association of exophthalmos with a toxic adenoma of the thyroid, in which careful microscopic examination failed to disclose any hyperplasia. Although it is quite possible that such a relationship has been commented upon previously, a careful survey of

the recent literature, and standard texts, discloses no such record.

A married woman, aged 41 (Case No. 129,754, University of California, Out-Patient Department, Ductless Gland Clinic), consulted us October 25, 1926. She complained of prominence of the eyes and nervousness. There was no family history of goitre and her past history was of no significance, except for the fact that she resided in Sweden until 24 years of age, and in Illinois, between 24 and 31 years of age. From 31 until the time we saw her, her residence was in Berkeley, California, a region in which the endemic incidence of goitre is negligible. Six months ago the patient's friends noticed that her eyes were becoming prominent. This ocular protrusion progressively increased. During this time she also had frequent headaches, more severe at night, and worse over the left eye.

Since the birth of her baby, 18 months before, she had been very nervous with a tendency to cry. She also experienced palpitation frequently. Perspiration was somewhat increased. The appetite, though good, was not excessive. She had lost five pounds in the previous six weeks, but this was probably related to a pan-hysterectomy for "fallen womb" and difficulty in holding urine.

The significant points in the physical examination were as follows: Her nutrition was good; skin was warm and moist; there was slight vasomotor flushing, but not the marked nervous instability ordinarily noted in Graves' disease. The exophthalmos produced an anxious and staring expression, but her demeanor was singularly placid in comparison to the agitated behavior ordinarily encountered in an individual with such pronounced exophthalmos.

The eyes were strikingly prominent, exophthalmos being greater in the left; Moebius' sign was slightly positive; Joffroy's and Dalrymple's doubtful, but Von Graefe's lid lag unmistakable. The upper lids were markedly edematous (see Fig. 1). The thyroid gland was not visibly enlarged and no thrill was palpable, nor was any bruit audible. Its consistency was firm but not nodular. The heart was not enlarged; the sounds were of good quality and only slightly "toxic." The pulse rate was 88; blood pressure, 140/80.

In short, here was a patient who exhibited pronounced exophthalmos without the usual clinical findings of Graves' disease. Moreover, from a clinical standpoint, the patient was but mildly toxic, and this was subsequently confirmed by a basal metabolic rate of only 26.5 per cent plus. In other words, the exophthalmos was out of all proportion to the relatively mild thyrotoxicosis. It therefore seemed to us unlikely that the patient could be suffering from true exophthalmic goitre (Graves' disease). It is true that mild exophthalmos sometimes persists despite considerable abatement of the toxic process, and remains then as a grim reminder of a previous wave or peak of toxicity, which has either spontaneously diminished, or been reduced by roentgen rays or thyroidectomy. The anamnesis, however, clearly demonstrated that there had been no such earlier period

of intense toxicity. Indeed the exophthalmos itself was of comparatively recent onset.

We suspected that the protrusio bulborum had some other explanation and a skiagram of the chest revealed a shadow extending one inch posterior to the sternum, suggestive of a substernal goitre. We were therefore inclined to interpret the exophthalmos as due to the pressure of this substernal goitre on the cervical sympathetic chain, and predicted that this intrathoracic extension would probably be an adenoma, since this is predominantly the type of goitre found within the thorax.

Fig. 1. Patient before operation. Fig. 3. Same patient four months after operation.

Others on the medical service and the surgical consultants, favored the customary syndrome of exophthalmic goitre. Indeed, the opinion of the writers was regarded as rather fanciful. A subtotal thyroidectomy was done. Preliminary exploration, before resection of the gland, did not disclose any substernal extension, but just before closing, when the field was more accessible, further investigation revealed a large elongated nodule —8x3x3 cm. lying posterior to the trachea.

In view of the exceptional interest that attached to this case, especially thorough miscroscopic studies of the excised

tissue were made by Doctors E. I. Bartlett and R. J. Millzner. Their report follows:

*Gross pathology:* The specimen is a thyroid consisting of 4 pieces measuring, respectively, 8x3x3, 5x3.5x2, 4x3x2, and 2x1x1 cm. The total weight is 48 grams The anterior surfaces are partly encapsulated and marked by skin clips. Other surfaces show the rough planes of resection. Cut surfaces show multiple small adenomas. In some places these are closely packed. All contain coarse colloid. The gland proper is semi-translucent with moderately divided colloid.

*Gross impression:* Multiple small, degenerating and nondegenerating adenomata of adult pattern in a normal thyroid gland.

*Microscopic pathology:* Sections of an adenoma show irregularly interspersed small to large alveoli lined by flat to low cuboidal cells and containing moderate colloid. A small amount of interalveolar epithelium is present. A few areas show separation of the alveoli by edema. Several small hemosiderin deposits from old hemorrhage are present. The gland proper shows moderate alveoli lined by flat epithelium and containing moderate colloid. The interalveolar epithelium is slightly increased. No lymphoid tissue is seen. There is an increased amount of connective tissue stroma.

*Diagnosis:* Multiple small, degenerating and nondegenerating adenomata of adult pattern in a normal thyroid gland (see Fig. 2).

Fig. 2. Low power microscopic photomicrograph showing adenoma and adjacent thyroid gland. Gland proper at the lower right hand corner. Note the inactive cells lining the alveoli of the gland proper. The rest of the gland shows the same picture.

The patient made an uneventful recovery and one month after operation had a basal metabolic rate of 10.6 per cent plus.

The exophthalmos gradually receded, and when last seen four months after operation was scarcely noticeable (See Figure 3). The basal metabolic rate at this time was 8 per cent plus.

## COMMENT

Exophthalmos may be due to inflammatory conditions or aneurysm within the orbit, or to intraorbital tumors; it has been noted in chronic cyanosis of the head from cerebral arteriosclerosis or aneurysm or nephritis. It may occur as a consequence of increased intracranial pressure [one of us (H. L.) has observed an outspoken case of acromegaly in which there was pronounced exophthalmus]. Finally, v. Müeller mentions its occurrence as a "toxic vasomotor condition in some cases of lead poisoning." In the overwhelming majority of cases in which exophthalmos is associated with goitre, the latter is of the hyperplastic variety (exophthalmic goitre, or Graves' disease). In a smaller, but by no means negligible minority, exophthalmos occurs in connection with "mixed" goitre, which is both hyperplastic and adenomatous; although in such cases the exophthalmos has been interpreted as resulting from the hyperplastic process.

## SUMMARY

Herewith is presented what appears to be an unusual relationship, namely, pronounced exophthalmos in a woman, consequent to the pressure of a substernal adenoma on the cervical sympathetics. The removal of this adenoma relieved the exophthalmos, and careful examination of the excised tissue failed to show any hyperplasia.

The rarity of this condition seemed to justify its publication.

# Book Reviews

ENDOCRINOLOGIE. Zentralblatt für der Gebiet der innere Secretion und Konstitutionsforschung. Originale und Referate.

It is a pleasure to note the establishment of a new journal in German devoted to endocrinology and constitutional studies. Volume I, No. 1, appeared in January, 1928, under the editorship of Professors Asher and Biedl, with Professor Hans Gunther of Leipzig as managing editor. It is published by Johan Barth, Leipzig. The initial number includes 5 original articles (44 pages) and 36 pages with selected abstracts. The journal is well printed and the illustrations are notably good. The bibliographic style follows the modern usage, giving exact references. Altogether, the first issue is a credit both to the editor and to the publisher.—R. G. H.

THE HISTOLOGY OF THE MORE IMPORTANT HUMAN ENDOCRINE ORGANS AT VARIOUS AGES. Eugenia R. A. Cooper. Oxford University Press, American Branch, N. Y. P. 119.

Reviewed in J. Lab. & Clin. Med. 13: 1080. 1928.

MONGOLISM. A STUDY OF THE PHYSICAL AND MENTAL CHARACTERISTICS OF MONGOLIAN IMBECILES. Kate Brousseau, and H. G. Brainerd, 1928. The Williams Wilkins Company, Baltimore. P. 210.

The authors have compiled and analyzed the statistics relative to this disorder, adding the results of ten years of intensive personal study. The book comprises sections on "general considerations," etiology, morphology, nervous and mental characteristics, diagnosis, prognosis and treatment. The book closes with 12 illustrative case reports and a twenty-page bibliography.

All of the well known ideas as to etiology are considered and all are rejected on statistical grounds except the endocrine theory, which is found to have some dubious basis. The conclusion is reached that no known form of direct treatment is of significant value.

The material is readably presented and the illustrations, graphs and tables are clear.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1926. Bd. I, Lief. II. Curt Kabitzsch, Leipzig. P. 336. Jaffe, R., F. Berberich and A. W. Fischer.

In a previous issue the publication of an extensive handbook on the internal secretions by German authors was announced. The second volume of the morphological group takes up the male sex glands. Jaffe and Berberich discuss the testis in an article of 84 pages. This is based on broad study of the literature—predominately German, but considering most of the outstanding contributions in other languages. The only outstanding omissions noted are Lillie's work on freemartins and the Japanese and American work on the effects of elevated temperature on the testes. The illustrations are notably good. The somewhat extensive literature on gland transplantation receives only two pages of discussion and the effect (or lack of effect) of testis extracts practically no discussion. Pathological changes in the testis and the relation of these to other endocrine organs, on the other hand, receive detailed treatment. Students in this field will find the article valuable but needing supplementing from other sources. It is concluded that the endocrine function of the testis is mediated by the spermatic rather than the interstitial cells.

Fischer's section (50 pages), on the prostate and other accessory sex gland structures, gives an excellent summary of the morphological features and serves to emphasize the paucity of data bearing on their endocrinology. His bibliography is excellent though somewhat slip-shod in form.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927. Bd. I, Lief. III. Curt Kabitzsch, Leipzig. P. 472. Berberich, J. and B. Fischer-Wassels.

This volume is devoted to the morphology of the thyroid and parathyroid glands. The former is treated in a section of 95 pages by Berberich and Fischer-Wassels. It gives a conventional treatment of such topics as embryology, comparative, microscopic and gross anatomy, etc. The local thyroid reactions to various diseases is interestingly discussed. Several of the illustrations in color are excellent. The chapter gives on the whole a fairly satisfactory account of the contributions in the German literature, but is otherwise practically useless to anyone desiring an adequate discussion of the literature as a whole.

The parathyroids are treated by the same authors in much the same way in a section of 40 pages. The literature list is, however, much more satisfactory in that English, French and Italian publications receive more adequate consideration.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1928. Bd. I, Lief. IV. Curt Kabitzsch, Leipzig. P. 708. Jaffe, R., I. Tannenberg and H. Josephy.

In this volume Jaffe and Tannenberg devote a section of 188 pages to a discussion of the morphology of the adrenals. The article is illustrated with several pleasing colored cuts. As in case of other organs dealt with in this part of the work, the embryology, comparative anatomy and gross and microscopic morphology, normal and pathologic, are treated. One of the most interesting sections is that devoted to the influences of inanition, avitaminosis, toxins, etc., on the glands. The condition of the adrenals in numerous diseases is discussed. This is followed by a section on diseases of the glands themselves.

The chapter is well written and each section is summarized. The literature cited is about eighty per cent German. The bibliography is somewhat slip-shod, the references being incomplete and, in some cases, translated into German.

In a section of 46 pages, Josephy discusses the normal and pathological anatomy of the vegetative centers of the mid-brain and of the sympathetic and parasympathetic nervous systems. To a considerable extent the material is dealt with on its own merits, irrespective of the endocrine glands, but, to a considerable extent, wherever any information is available, the correlation is drawn. The literature list is made up mostly of German titles.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927, Bd. II, Lief. I. Curt Kabitzsch, Leipzig. P. 275. L. Asher and M. Guggenheim.

In this volume in an article of 35 pages Asher discusses the comparative physiology of the internal secretions. He takes up first the general conception of internal secretion as a physiological process. He presents an interesting classification which includes not only the hormones, but nutritive substances, harmozones and parhomones. This, of course, brings in other structures than the endocrine glands, proper. Other topics considered are methodology and comparative dynamics. Perhaps the most interesting section is that devoted to the influence of physiological factors on the action of hormones. Dregstedt's fundamental work on the influence of anesthetics in the pharmacodynamics of adrenaline is not included—presumably because of its recent appearance. The section, while by no means exhaustive, affords a judicious introduction to the general subject treated.

The section on the chemistry of the internal secretions by Guggenheim runs to 132 pages, the last 32 of which are devoted to a most excellent bibliography. Each of the recognized endo-

crine organs is taken up seriatim and such knowledge as we have on the chemistry of each is set forth with admirable clarity. In refreshing contrast to some of the authors of the volumes previously noted, Guggenheim's bibliography shows a catholic acquaintance with the literature of his subject.

In an article of 86 pages Asher discusses succinctly and excellently the usual topics treated under "Physiology of the thyroid." His bibliography, though of only 6 pages, is excellently selected to include the most significant titles in the world's literature.

The same comments can be made on his article on the parathyroids. This comprises 22 pages.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1927, Bd. II, Lief. II. Curt Kabitzsch, Leipzig. P. 422. Aschner, B. and W. Lahm.

In an article of 98 pages, Aschner gives a good discussion of the physiology of the hypophysis. His own interest in that topic is manifest in the relatively undue space devoted to pituitary extirpation. The discussions and the bibliography alike show familiarity with the entire significant literature. The article is necessarily incomplete, but gives on the whole as good an account of the subject as could be expected in a hundred pages.

The rest of this volume is made up of negligible discussions of the pineal gland by Aschner; of the breasts, uterus, vagina and clitoris "as endocrine organs (!)" and of the placenta, by Lahm. The article on the placenta is notably inadequate, all the significant literature except that in German having been ignored.

EL BOCIO Y EL CRETINISMO. Gregorio Marañon, 1928. Paez, Madrid. P. 189.

Marañon presents a discussion of endemic goiter and cretinism as they occur in Spain. The book is illustrated with numerous interesting photographs. The topics chiefly covered are the distribution of the disorder, together with its pathogeny and prophylaxis. The book should not be overlooked by anyone interested in the broad field of endemic goiter.

DIABETES AND ITS TREATMENT BY INSULIN AND DIET. A handbook for the patient. Orlando H. Petty, 1928. F. A. Davis Company, Philadelphia. P. 155.

This little book is an excellent compendium designed for the education of the diabetic. The fact that it has gone to a fourth

edition speaks for itself. The obscurity of diction that was noted in a few instances in the first edition has been clarified. The book can be highly recommended.

INFANCY AND HUMAN GROWTH. Arnold Gesell, 1928. The MacMillan Company, New York. P. 418.

The book includes a 28-page chapter on glandular and nutritional factors in mental growth.

THE GLANDS REGULATING PERSONALITY. A STUDY OF THE GLANDS OF INTERAL SECRETION IN RELATION TO THE TYPES OF HUMAN NATURE. Louis Berman, 1928. Second Edition, Revised. The MacMillan Company, New York. P. 329.

The following excerpts represent the central theme of this book:

"The life of every individual, in every stage, is dominated largely by his glands of internal secretion. That is, they, as a complex internal messenger and director system, control organ and function, conduct and character. The orderliness of human life, in the sequential march of its episodes, crises, successes and failures, depends, to a large extent, upon their interactions with each other and with the environment.

"One or several of the glands possesses a controlling or superior influence above that of the others in the physiology of the individual, and so becomes the central gland of his life, its dominant, indeed, so far as it casts a deciding vote or veto, in its everyday existence and incidents as well as in its high points, the climaxes and emergencies.

"These glandular preponderances are determining factors in the personality, creating genius and dullard, weakling and giant, Cavalier and Puritan. All human traits may be analyzed in terms of them because they are expressions of them.

"Specific types of personality may be directly associated with particular glandular prominence, so that we have the thyroid-centered type, the pituitary-centered type, the adrenal-centered types, etc. These are the prototypes in their purity most easily described and recognized.

"Gay vivacity and grim determination, the temperament of a Louis XIV and the soul of a Cromwell, are the crystallizations of these chemical substances acting upon the brain."

Excellent entertainment—brilliant speculation—mostly exaggerated, but harmless if one does not swallow it whole. The unfortunate aspect of this book consists in the appeal that it

will have for the laity. Imaginative theorizing becomes dangerous when expressed as if it were established fact.

THE ENDOCRINES IN GENERAL MEDICINE. A. Langdon Brown, 1927. Paul B. Hoeber, New York. P. 134.

Reviewed in Arch. Int. Med. 42: 148-149. 1928.

METHODS OF BIOLOGICAL ASSAY. J. H. Burn, 1928. Oxford University Press. P. 126.

The book contains descriptions of methods of biological assay of pituitary (posterior lobe) extract, insulin, adrenalin, ovarian œstrus-producing hormone, parathyroid hormone, thyroid extract and anterior lobe of the pituitary gland.

INNERE SEKRETION IN DER ERSTEN LEBENSZEIT (vor und nach der Geburt). Thomas, E. 1926. Gustav Fischer, Jena. Pp. 194.

# Abstract Department

**The comparative effect of epinephrin upon blood pressure and intestinal motility in the dog.** Dragstedt, C. A. and J. W. Huffman. Am. J. Physiol. **85**: 129. 1928.

The simultaneous effects of continuous injections of epinephrin on blood pressure and intestinal motility were recorded in dogs during and after anesthesia with ether, under morphine, under paraldehyde, and in the absence of drugs and anesthetics. It was found that with a certain amount of ether and in three instances with barbital, trional and amytal the blood pressure would be raised at the expense of intestinal motility. In normal animals and in dogs under morphine, paraldehyde or after stunning, the opposite relationship obtains. In these conditions considerable rises in blood pressure can be obtained without intestinal inhibition.

—Authors' Abst.

**The blood pressure of adrenalectomized rats.** Durant, R. R., Am. J. Physiol. **85**: 364. 1928.

The adrenals were removed from 20 female rats, approximately two years old and varying in weight between 157 grams and 400 grams. The blood pressure of 11 of these animals determined by the direct method within the first 5 hours following the operation varied considerably with extremes of 85 mm. and 145 mm., and an average of 112 mm. Hg. The last figure has been found previously to be the average pressure for normal rats of the same age. The blood pressures of the remaining 9 animals, determined 6 hours to 22 days after the extirpation, were low, with a minimum of 52 mm., a maximum of 95 mm., and an average of 77 mm. Hg. Ten animals of the same age and of both sexes were operated as controls. Two had one adrenal removed, another had one whole capsule and all but a small piece of cortex of the other removed. A sham operation simulating the adrenalectomy was performed upon the remaining seven. The pressures of this group were found to vary between 65 mm. and 135 mm., with an average of 104 mm. Hg. Eliminating the data obtained upon 2 animals, which at autopsy proved to be in very poor condition, the average pressure for the control group is 111 mm. Hg. The three animals that had undergone partial adrenalectomy possessed the normal pressure. These observations indicate that in rats adrenalectomy has no immediate effect

upon blood pressure, but that after 6 hours a marked fall in pressure occurs and that the adrenals through either their cortical or medullary components are concerned in the maintenance of normal pressure.—Author's Abst.

**The action of epinephrin upon the capillaries and fibers of skeletal muscle.** Hartman, F. A., J. I. Evans and Helen G. Walker. Am. J. Physiol. **85**: 91-98. 1928.

Seventy cats of various ages and 2 rabbits were studied while under the influence of ether, urethane or else decerebrated. The microscopic changes of either the sartorius of the tibialis anticus were observed with transmitted light. Adrenalin ranging from 0.2 cc. of 1:100,000 to 1 cc. 1:10,000 was injected into the jugular vein. Ether caused a marked dilatation of the capillaries, an increase in blood flow and haziness of the field. Adrenalin caused dilatation of capillaries, venules, arterioles, veins and arteries, and an increase in blood flow with small doses. Later congestion and a slower rate of flow might occur. The whole field became clearer and brighter. Cross striations in the muscle fibers became visible or better defined. Also transverse twitching or vibration of the muscle fibers might appear. These effects lasted as long as seven minutes. With larger doses (1 cc. or more of 1:100,000), the capillaries and very small vessels dilated as before, while the veins, arteries and arterioles constricted. The transparency and twitching became more marked. Muscle denervated only a few hours shows little change in the capillaries in response to adrenalin because dilatation is already great. If several days elapsed after denervation, the adrenalin reaction resembled that in the normal, except that it was unstable. Adrenalin twitching was absent or poorly developed.

—Authors' Summary.

**Suprarenal insufficiency: Report of two cases.** Marsh, H. E., Am. J. M. Sc. **175**: 769-777. 1928.

A biographical sketch of Addison is given and a survey of his investigation of the disease which bears his name. Two cases are presented which clinically conform to Addison's disease. Both patients improved under substitutional therapy and are still living. Both had recurrence of symptoms whenever treatment was discontinued.—Author's Summary.

**Rat activity and adrenalin.** Nice, L. B., D. S. Greenberg and S. L. Greenberg. Am. J. Physiol. **85**: 397. 1928.

The activity of three groups of rats was studied. A normal group was given 1 cc. of 1:50,000 adrenalin chloride hypodermically daily; to a second group of adrenalectomized rats was administered an equal amount of adrenalin in the same way, while a third group of adrenalectomized rats was not injected. The spontaneous

activity of the normal rats was decreased on the whole, while the activity of the injected adrenalectomized rats closely paralleled that of the non-treated group.—Authors' Abst.

**Adrenal insufficiency: The beneficial influence of cortical adrenal extracts in adrenalectomized animals.** Rogoff, J. M. and G. N. Stewart, Am. J. Physiol. **85**: 404. 1928.

Administration of adrenal cortical material prepared by extraction, in various ways and with various solvents, is capable of prolonging life of completely adrenalectomized animals well beyond the maximum period of survival of control, untreated adrenalectomized animals. In animals which do not live beyond the maximum period of survival of adrenalectomized, untreated controls, as well as those which exceed this period, the usual symptoms are generally ameliorated.—Authors' Abst.

**Effect of haemorrhage upon the rate of liberation of epinephrine from the suprarenal gland of dogs.** Saito, S., Tohoku J. Exper. Med. **11**: 79-115. 1928.

Experiments were made on 8 control dogs, on 16 anesthetized and on 11 de-afferented dogs. Adrenal blood was collected in vena cava pockets and assayed by means of the rabbit intestine method. It was found that with the dogs under ether the loss of 1/5 of the total quantity of blood called forth a small but definite augmentation in the secretion rate of adrenalin. The bleeding of 1/10 was not certain to cause the hypersecretion of epinephrine. In the experiments on the non-fastened, non-anaesthetized de-afferented dogs the loss of 1/15 of the total blood quantity was usually effective in evoking the increase, though weak, of epinephrine discharge. When 1/10 of the whole blood was lost, the velocity of liberation two to ten times as rapid as the initial was invariably noted, and the hypersecretion continued for about three hours. When 1/3 or 2/5 of the total amount was shed, the output rate ten to thirty times as quick was noted, and the hyperactivity of the medulliadrenal gland lasted for a considerable length of time. At the fourth or sixth hour after the bleeding the epinephrine secretion had a definitely exaggerated velocity. In general, the greater the haemorrhage, the greater and the longer the hypersecretion of epinephrine from the suprarenal capsule. For the material difference between the two sets of experiments above mentioned the narcosis is responsible, at least chiefly.—R. G. H.

**Studies on the conditions of activity in endocrine glands. XXIV. Asphyxial stimulation of the denervated adrenal gland.** Zwemer, R. L. and H. F. Newton, Am. J. Physiol. **85**: 507-511. 1928.

Asphyxia of the denervated adrenal, induced by compression of the aorta near the diaphragm for ten seconds was found in 7

cats to cause a discharge of adrenin, as shown by a large increase in the rate of the denervated heart. Demedullation of the adrenal prevented the increase in heart rate after asphyxia. It was concluded, therefore, that the denervated adrenal medulla can still respond to asphyxial stimulation.—R. G. H.

**The function of the carotid body. Relation to the carotid sinus reflex (Sur la fonction de la glande [paraganglion] carotidienne. La glande et le réflexe du sinus carotidien).** Jacobovici, J., I. Nitzescu and A. Pop, Compt. rend. Soc. de biol. **98**: 640-643. 1928.

Hering has described a reflex fall of blood pressure following pressure in the region of the carotid sinus. Experiments in five cases on man indicate that this reflex is due to stimulation of the carotid body (glomus caroticum).—J. C. D.

**The peripheral control of blood sugar by drugs (Die periphere Steuerrung der Blutzuckerreal auf Gifte).** Bertram, F., Arch. f. exp. Path. u. Pharmakol. **126**: 267. 1927. Abst., Physiol. Absts. **13**: 174.

The effect of various agents on the blood sugar is fully reviewed. Calcium, acids, and thyroid preparations increase the hyperglycaemia due to adrenaline or food, and diminish hypoglycaemia due to insulin. Potassium and alkalis have the reverse effects. None of these agents has per se much effect on the normal blood sugar. On the other hand, the hyperglycaemia due to pilocarpin is increased by potassium and lowered by calcium. It is also, however, increased by acids and thyroid.

**Calcium metabolism in skin diseases.** Burgess, N., Brit. J. Dermat. **40**: 279. 1928. Abst., J. A. M. A. **91**: 525.

The discovery made by Burgess of a normal figure for the total serum calcium in association with a diminished amount of precipitable calcium in many cases, and a diminution of both total and precipitable calcium in a few cases of certain skin diseases, confirms the work of Vines and Grove. Cases of urticaria, especially those showing marked dermographism, prurigo of the Besnier type, total alopecia areata, light sensitization of the adult type, and eczema, in the vast majority of instances present a marked diminution of precipitable serum calcium. Cases of acro-asphyxia and erythema pernio can be divided into two groups—those showing a greatly diminished precipitable calcium, and those in which the serum calcium is normal. Cases of urticaria, prurigo, eczema and those cases of acro-asphyxia and chilblains with a low serum calcium were considerably improved by treatment with calcium and parathyroid. Only one case of sporiasis showed a diminished precipitable serum calcium. Two patients with seborrheic dermatitis out of five had a

lowered serum calcium, accompanied by much secondary infection. A slight diminution of the serum calcium was found in one case of erythema multiforme, while normal figures were obtained in a case of Darier's disease and a case of acrodermatitis continua. Of the cases investigated, those in which the endocrine glands and sympathetic nervous system are believed to be primarily at fault showed a diminution of the precipitable calcium in the serum, while in most cases the total calcium was found to be normal. It is believed that the dysfunction of the endocrine glands leads to an alteration in the chemical or physical state of the calcium in the serum, so that there is a diminution in the amount of calcium which can be used by the tissues. This is believed to cause an increased irritability of the sympathetic nervous system which leads to the formation of skin lesions.

**Testicular grafts in Triton. Fresh experimental evidence that the sex cells do not control secondary sex characteristics (Greffes testiculaires chez les Tritons. Nouvelle preuve expérimentale du fait que les cellules de la lignée séminale n'exercent aucune action sur les caracteres sexuels).** Aron, M., Compt. rend. Soc. de biol. **98**: 845-847. 1928.

In this urodele the sex cells, spermatogonia, and Sertoli cells develop first and later, into spaces made vacant by discharge of spermatazoa, grow glandular cells corresponding to the interstitial cells of mammals. Animals were castrated and then grafted with testes from other Tritons. In a number of cases these animals developed normally, while others showed no secondary male characters. In the first group, autopsy showed that the grafts had made connections with the duct system; that spermatazoa had been discharged and the interstitial gland had developed. In the latter no connection had been made, the spermatazoa and other cells of the testes were present, but the development of the interstitial gland had been inhibited and it was absent. It is the interstitial gland cells, not the sex cells, which control the secondary sex characters.

—J. C. D.

**Influence of castration on metabolism (both basal and maximum) (Action de la castration sur le métabolisme énergétique [Métabolisme de base et métabolisme de sommet]).** Chahovitch, X. and Mlle. M. Vichnjitch. Compt. rend. Soc. de biol. **98**: 1153-1155. 1928.

Castration reduces the metabolic rate in rats.—J. C. D.

**The clinical use of ovarian follicular hormone with special reference to functional sterility.** Hirst, J. C., II, Am. J. Obst. & Gynec. **15**: 487. 1928.

In 5 of 12 cases of sterility, conception occurred after a course

of injection of ovarian follicular hormone. Three of 5 subjects with menstrual disorders were benefitted by the hormone.

—M. O. L.

**The effect of injection of follicular extract on the sex organs in guinea pig and interaction between follicular substances and substances given off by corpus luteum.** Loeb, L. and W. B. Kountz. Am. J. Physiol. **84**: 283-306. 1928.

Injections of follicular extract in immature guinea pigs accelerate the maturation of follicles; similarly in under-fed guinea pigs, they delay the hypotypical state of the ovaries or diminish the intensity of this process and thus allow the better development of the follicles as compared to the condition in undernourished, but not injected, controls. Otherwise injection of follicular extract does not accelerate noticeably the maturation of follicles or to increase the number of mature follicles. Injection of follicular extract prevents ovulation in the guinea pig and must therefore lead to sterility as long as the injections are continued. The large, persistent corpus luteum, as it exists in hysterectomized and pregnant animals, tends to counteract the acceleration effects of the injections on the opening of the vagina and the proliferation of the vagina under the influence of the injections. These investigations thus confirm and bring out still more definitely the difference in the effects of the large, persistent corpus luteum on the one hand and of the small cyclic corpus luteum on the other hand. The injections of follicular extract have in general only very slight effects on the uterus of the guinea pig; they cause hyperemia, slight local edema and some hemorrhage of the mucosa; in a few cases marked oestral changes in surface epithelium, neck of the glands and connective tissue were observed. Neither does the follicular substance cause the predecidual proliferation or the uterine mucosa, which is produced by the corpus luteum at a certain phase of the normal cycle, but on the contrary, it tends to prevent this effect. On the other hand, the corpus luteum does not cause the proliferation of the vagina which is called forth by the follicular substance; it tends rather to prevent this effect. It is concluded that the ovarian follicles and corpus luteum contain or give off substances which are not identical. Some of the effects of these substances on the sex organs are different, while others are similar.—Authors' Summary (abbreviated).

**Experiments on isolated ovaries (Versuche an isolierten Eierstöcken).** Nikolaeff, M. P., Ztschr. f. d. ges. exper. Med. **54**: 32-57. 1927. Abst., Biol. Absts. **1**: 1059.

In specimens of cow's ovary and broad ligament from the abattoir, the ovarian artery and vein were cannulated, collateral vessels ligated, and the ovary perfused with oxygenated Ringer-Locke solution at body temperature. The perfusate was collected and tested

pharmacologically. During perfusion the broad ligament undergoes periodic spontaneous contractions, varying in type in the pregnant and non-pregnant cow. The perfusate, at first slightly acid, becomes neutral as perfusion is continued, and contains a small amount of protein. It usually increases the amplitude of contractions of the isolated frog's heart, while slowing the rhythm; and usually raises the blood-pressure of dogs. In low concentration this fluid raises tonus and increases contractions of isolated cat's intestine; concentrated dosage gives an opposite effect. On the isolated cat's uterus it acts strikingly, increasing tonus and giving the contractions a tetanic character. Release of adrenalin-like substance from the isolated adrenal is increased by the ovarian perfusate.

**The influence of prostatectomy on the sex life of the male albino rat.** Patterson, T. L., Am. J. Physiol. **85**: 398. 1928.

Removal of both the seminal vesicles and the prostate from male rats produces absolute sterility, but it has not been determined if sterility follows complete prostatectomy alone. Young male rats prostatectomized at five to six weeks of age, mated with normal females, and observed over a period of twenty months were sterile, but this only occurs when the extirpation of the gland is complete, as evidenced by histological studies. The sexual instincts and sexual activity develop in these animals normally, though with some delay, which is probably due to operative interference in a region very sensitive to injury. This indicates that the development of the somatic sex characters and of the psycho-sexual behavior is independent of the presence of the prostate and of any endocrine function of this organ.—Author's Abst.

**Extraction of ovarian hormone from urine.** Veler, C. D. and E. A. Doisy. Proc. Soc. Exper. Biol. & Med. **25**: 806-807. 1927-28.

Description of the procedure used in the extraction of the ovarian hormone from urine. From 500-1,200 rat units per liter were obtained from the urine of pregnant women. Post-partum urines contain very little of the hormone 48 hours after delivery.
—E. A. Doisy.

**Consequences of castration and of eunuchoidism in man (Beiträge zur Kenntnis der Kastrationsfolgen und des Eunuchoidismus beim Mann).** Wagenseil, F., Ztschr. f. Morphol. u. Anthrop. **26**: 264-304. 1927. Abst., Biol. Absts. **1**: 1067.

Observations were carried out on 11 eunuchs (natives of Sudan and Abyssinia) castrated at the age of 7-12. In most cases even the external genitalia were removed. Two eunuchs died of typhus and were used for histological studies. The author considers the gonads necessary for the onset of puberty, either directly or perhaps through other glands of internal secretion, but his pathologic-

anatomical findings do not seem to support the latter contention. Changes were noted only in the hypophysis, which showed eosiniphilia, and in the thymus, the epithelial parts of which underwent hyperplasia. The thyroid was generally reduced in size. In a tall eunuch the x-ray picture revealed a large sella turcica, indicating an enlargement of the anterior lobe of the hypophysis. The author cannot confirm Koch, who believes that age at castration is important in the differentiation of various types of eunuchs, and thinks that the reactions of the ductless glands to castration vary with the individual; also he does not believe that the adiposity of eunuchs is always due to pituitary involvement. He agrees with Falta, who differentiates between pituitary and genital dystrophia adiposo-genitalis, and believes that the adiposity is due solely to the absence of the internal secretion of testes. The author autopsied and examined histologically a eunuchoid Turk. Testicles and other genitalia, heart, and appendix showed embryonic characteristics. He regards eunuchoidism as of idiotypic origin, being closely related to or identical with infantilism. Symptoms of eunuchoidism are ascribed to a hypofunction of the gonads, and there is believed to be no evidence that the hypophysis is responsible.

**On bitemporal contraction of the visual field in pregnancy.** Abramowicz, I., Brit. J. Ophth. **11**: 17-27. 1927. Abst., Biol. Absts., **1**: 1060.

In few cases of normal pregnancy (6 per cent) there occurs in the last month of pregnancy a slight temporal contraction of the visual field, which may be occasioned by the hypertrophy of the pituitary body. On the tenth day after delivery the visual field returns to normal.

**Diuretic-antidiuretic effect of the pressor principle of the posterior lobe of the pituitary gland.** Bugbee, E. P. and A. E. Simond. Am. J. Physiol. **85**: 357. 1928.

It has been demonstrated that the posterior lobe of the pituitary gland contains two active principles, one which contracts uterine muscle and the other which raises blood pressure. We were interested in finding out if the diuretic-antidiuretic effect is associated with one of these or is due to still another active principle. Experiments have been made on rabbits under urethane, amytal, chloralhydrate and chloretone anesthesia. It was found that the oxytocic principle has little effect upon the flow of urine, determined by counting the drops falling from a cannula in the bladder. The pressor principle causes first a decrease in urine flow, then a copious flow of short duration, followed by diminished excretion. The relative intensity and duration of these three effects vary in different rabbits and depend upon the depth of anesthesia and upon the dosage of pressor principle. Renal function tests on rabbits have been made in a manner similar to the commonly used clinical

phenolsulphonephthalein test. It has been found that the oxytocic principle has little effect upon the excretion of dye, whereas the pressor principle diminishes the rate of excretion of the dye.
—Authors' Abst.

**Posterior pituitary lobe extract: its action on water excretion in normal cases, cases with diabetes insipidus, and cases with sclerotic kidneys (Action de l'extrait du lobe posterieur de l'hypophyse sur le metabolisme de l'eau, chez l'homme normal, dans le diabete insipide et la sclerose renale).** Coelho, E., Compt. rend. Soc. de biol. **98**: 469. 1928.

Subcutaneous injections always reduce the output of urine.
—J. C. D.

**The antidiuretic effect of the oxytocic and pressor principles of the extract of the posterior lobe of the pituitary.** Gargle, S. L., D. R. Gilligan and H. L. Blumgart. New England J. of Med. **98**: 169. 1928.

Kamm has recently separated the extract of the posterior lobe of the hypophysis into two parts. Oxytocin has an oxytocic action and vasopressin a pressor action. The authors summarize their clinical studies as follows: In four normal men, single doses of vasopressin checked the excretion of a liter of water for five or six hours, while oxytocin had but slight effect. In two patients with diabetes insipidus, vasopressin effectively controlled the thirst and polyuria, while oxytocin proved ineffective. Intranasal administration of vasopressin by cotton pledget proved more effective than subcutaneous administration in the two patients with diabetes insipidus. On the basis of these findings the antidiuretic effect of extracts of the posterior lobe of the pituitary gland seems to be inherent in the pressor principle.—J. C. D.

**The active principles of the posterior lobe of the pituitary gland. I. The demonstration of two active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations.** Kamm, O., T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Bugbee, J. Am. Chem. Soc. **50**: 573. 1928.

A substantially complete separation of two active principles of the posterior lobe of the pituitary has been accomplished by the employment of salting-out methods and, subsequently, by use of appropriate solvents and precipitants. One of these active principles raises blood pressure and the other stimulates contraction of uterine muscle. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (beta-hypophamine) has been obtained in the form of a white, stable, wa-

ter-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (alpha-hypophamine) has been observed in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Powdered Pituitary. The pressor principle has been shown to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies, presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones, and they have been made available to the medical profession for careful clinical trial.—M. O. L.

**Roentgen-ray treatment of pituitary tumors.** Sharapov, B. I. and V. I. Jutchenko. Physiotherapia, **2**: 80. 1927. Abst., J. A. M. A. **91**: 136.

Sharapov and Jutchenko report the results obtained with roentgen-ray treatment in forty-nine cases of tumors of the pars anterior of the hypophysis, characterized by more or less prominent symptoms of acromegaly. The first beneficial effect noted is the disappearance or diminution of symptoms due to pressure on the chiasma, enlargement of the field of vision and improvement of vision. Symptoms of increased brain pressure, headaches and vomiting are improved or disappear. At a later date, there is a return of the sexual function, manifested in women by the return of menstruation, in men by the return of potency. Coincident with this is a loss in weight. The enlarged extremities do not return to a normal state, but a relative diminution in size was observed in some of the cases. Apparently adenomas only are destroyed by the rays. Teratomas, cysts and gummas do not yield to the treatment. In the beginning there may be an exacerbation of symptoms, which, however, should not deter one from continuing the irradiations.

**Study of a substance in desiccated tissues which increases sugar utilization more than insulin.** Burge, W. E., A. M. Estes and G. C. Wickwire. Am. J. Physiol. **85**: 357-358. 1928.

The effect on sugar utilization of a great number of substances, such as the optically active and optically inactive amino acids, aminoids, ovarian and testicular substances, insulin, pituitrin, thyroxin, adrenalin, alcohol, inorganic salts, ether, chloroform, nitrous oxide and ethylene, has been studied. This investigation is concerned particularly with the effect of commercially prepared desiccated tissues, such as aminoids, a commercially prepared meat digest with an amino nitrogen of 7.5 per cent amino acids, desiccated testicular and ovarian substances. One hundred milligrams of each of these

materials, as well as varying amounts of insulin, were added to 100 cc. of a 0.1 per cent dextrose solution in beakers. Two gold fish, with a combined weight of five grams, were introduced into each of the beakers and air was kept bubbling through the liquid to insure an adequate supply of oxygen. Sugar determinations were made immediately and after thirty hours. It was found that the aminoids produced a greater increase in sugar utilization than the amino acids taken singly or collectively. The desiccated ovarian and testicular substances greatly increased sugar utilization. Desiccated thyroid increased sugar metabolism, while thyroxin did not. Insulin increases sugar utilization, but to a less extent than the desiccated tissues. The view is advanced that none of these desiccated tissues per se increases sugar utilization, but that they contain a substance which is responsible for the stimulating effect on sugar metabolism.
—Authors' Abst.

**Insulin does not increase the binding power of blood cells for glucose. Refutation of this theory of glycemia (L'Insuline n'augmente pas la fixation des glucides sanguins par les globules. Refutation de la notion de glycémine).** Fontès, G. and L. Thivolle. Compt. rend Soc. de biol. **98**: 847-849. 1928.

Loewi and others regard the blood sugar balance as determined by "glycémine," a substance arising in the liver and causing glycemia, and insulin. The test for the relative amounts of these substances is based on the supposed increased binding power for glucose of the blood cells in the presence of insulin. This paper gives extensive tables from observations on man and other animals showing that insulin does not influence the blood cells in this way.
—J. C. D.

**Latent tolerance in diabetes mellitus.** Gibson, R. B., Am. J. Physiol. **85**: 375. 1928.

Diabetics desugarized on maintenance diets with a F. A.: G. of 1.5 and the required insulin have shown remarkable improvement following high sugar ingestion with increased insulin. Two to three days of high sugar ingestion, with intervals of routine management in series, increases the tolerance until dietary management without insulin may suffice to control the diabetes; the most severe cases may require a greatly diminished insulin dosage. The procedure is especially effective in younger patients.—Author's Abst.

**Hypertension and diabetes.** Kramer, D. W., Am. J. M. Sc. **176**: 23-31. 1928.

The frequency of hypertension in diabetes is more common than we have been led to believe. In this study of 500 consecutive cases of diabetes, 195 patients (39 per cent) showed a blood pressure of 150 mm. mercury or above. The presence of hypertension in

diabetics may be attributed to various factors: the pathogenesis of these conditions is practically the same, and they are apt to appear in those past middle life, the highest percentage occurring in the sixth decade. This was evident in both series, 36.2 per cent in the diabetic group, and 39.1 per cent in the hypertensive non-diabetic group. Individuals with persistent hypertension of the non-nephritic type may in time develop diabetes. It is unlikely that diabetes, through its hyperglycemia, produces hypertension.

—Author's Summary.

**The absorption of insulin from Thiry Vella fistulae in normal and depancreatized dogs.** Murlin, J. R. and Ruth E. Latta. Am. J. Physiol. **85:** 397. 1928.

The results indicate that fistulae prepared several months before being used for experiments with insulin absorb the hormone better than freshly prepared fistulae. Weak alkalis up to 20th normal favor absorption. Weak HCl up to 100th normal does not retard absorption, but greater strength does in most of the tests. Blood serum retards the destruction of insulin by pepsin-HCl. This is due to the buffering effect of the serum proteins on the acid. When acid stronger than N/40 is used with ox-blood serum, there is destruction of insulin by pepsin. Blood serum alone or serum and HCl up to N/70 does not prevent destruction of insulin by trypsin.—Authors' Abst.

**Large ulcers of the leg of fourteen years' duration healed within twenty days with insulin pommade (Vastes ulcères de jambe datant de 14 ans et guéris en 20 jours par la pommade à l'insuline).** Pautrier, L. M. and Mlle. Ullmo. Presse méd., **36:** 58. 1928.

The authors call attention again to the treatment of ulcers of the leg with insulin. The work comes from the skin clinic at Strasbourg. The patient was 64 years of age with a glycemia of 1200 mgm. per 100 cc. and had had these ulcers for the past 14 years. The ulcers cicatrized completely in 20 days following the use of insulin paste.—H. J. J.

**Difficulties in diagnosis of insulin coma.** Sevringhaus, E. L., J. A. M. A. **91:** 305-307. 1928. Abst., A. M. A.

The author reports two cases of diabetes mellitus as examples of the difficulties that may occur in the diagnosis of coma due to an excess of insulin. They illustrate the necessity for the diagnosis of the cause of coma by clinical observation and the simplest laboratory aids, such as tests for urine sugar and acetone. They also call attention to the necessity for a therapeutic test to decide the presumptive diagnosis when the insulin reaction is not of the usual type, with sweating and hunger. When there is doubt as to the nature of a coma in a diabetic patient, there is nothing to be lost and much

to be gained from the therapeutic test of an intravenous injection of from 10 to 20 cc. of 50 per cent dextrose. This is so readily available in sterile form, and can be given with such ease, that it should always be at hand. In insulin coma it has repeatedly given results in from one to three minutes. The diabetic comatose patient will not respond, nor can any further harm be done by the single injection. If the coma does not respond to the dextrose within at least ten minutes, it would then be safe to proceed with the usual measures for treatment of true diabetic coma. Insulin coma yields quickly to intravenous injections of dextrose unless there is a complicating factor. The two cases presented illustrate the manner in which nervous excitement, unaccustomed exercise, or omission of food usually eaten, may induce severe reactions when they are not otherwise expected. The diagnosis was made uncertain because of suspected cerebrovascular syphilis in one case and the fear of a developing meningitic infection in the other. The therapeutic test of administering dextrose intravenously for relief of coma which may be due to insulin should be made.

**Acromegaly and diabetes.** Yater, W. M., Arch. Int. Med. **41**: 883-912. 1928.

A brief summary of the results of the main experimental and clinical investigations on the question of the relationship of the pituitary gland to carbohydrate metabolism has been given. Six more cases have been recorded of the interesting combination of acromegaly and diabetes mellitus, in 3 of which insulin was required. In one of these cases the diagnosis of acromegaly is admittedly questionable. Four others of a series of 79 cases of acromegaly showed some disturbance of carbohydrate metabolism, but this feature was not carefully studied in them. The diabetes in the 6 cases reported was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy. Three of the patients presented the unique complication of increased basal metabolic rate, in all three of whom it was presumably due to hyperthyroidism.—Author's Summary.

**Relation of parathyroidectomy to voluntary activity in the white rat.** Durrant, E. P., Am. J. Physiol. **85**: 364. 1928.

Observations by means of revolving activity cages on both unilaterally and bilaterally parathyroidectomized rats, 90 to 100 days old, show that though tetany is equally pronounced after both operations, the activity is merely temporarily depressed; but the recovery is much more rapid following the unilateral ablation. In rats 200 to 210 days old the results are the same qualitatively, but are more variable in amount.—Author's Abst.

**Vater Pacinian corpuscles in the parathyroid glands of guinea pigs (Sur l'existence de corpuscles de Vater-Pacini dans les glandes**

**parathyroides du Cobaye).** Florentin, P., Compt. rend. Soc. de biol. **98:** 1133-1135. 1928.

The sensory end organs are found fairly constantly in the guinea pig parathyroids.—J. C. D.

**Vago-cardiac irritability following guanidine intoxication and in parathyroid tetany.** Stoland, O. O. and W. Potter. Am. J. Physiol. **85:** 408. 1928.

The influence of guanidine carbonate and methyl guanidine upon the inhibitory action of the vagus upon the heart was studied in frogs, turtles and dogs. In frogs and turtles it was shown that the guanidines in sufficient dosage invariably block the inhibitory vagus action upon the heart. This block can easily be removed following a few minutes' washing with Ringer's solution. In dogs, doses of 25 mgm. or less per kgm. of body weight, injected intravenously, generally increased the vagus response to electrical stimulation. The same is true for larger doses injected subcutaneously or very slowly intravenously. Moderate doses 50 to 60 mgm. per kgm. body weight in most cases bring on a temporary but marked depression of vagus response to electrical stimulation. This period of depression may be shortened by administration of calcium salts. Larger doses, 100 mgm. per kgm. body weight, usually cause profound depression of vagus activity, sometimes accompanied by cardiac irregularities. The irritability of the vagus in dogs suffering from parathyroid tetany was found to vary from normal to fairly marked depression. If this is due to the presence of guanidine or its salts, the amount present must be rather large. To determine whether other parasympathetic mechanisms are affected by guanidine similarly to the vagus, we studied their effect upon the chorda tympani. We found that in 17 out of 18 dogs 100 mgm. methyl guanidine sulphate per kgm. body weight distinctly increased the secretion of saliva. This secretion is blocked by atropine. Response to electrical stimulation of the chorda tympani following the guanidine injection was lessened in 4 cases, increased in 2 cases and not affected in 2 cases. Our results indicate that guanidine in small doses increases the irritability of parasympathetic nerves, while larger amounts tend to depress the mechanism.—Authors' Abst.

**Symptoms and treatment of malignant goiter.** Barthels, C., Beitr. z. klin. Chir. **142:** 711. 1928. Abst., J. A. M. A. **91:** 62.

In 2,272 cases of goiter, malignant tumor of the thyroid was found in 112 cases. In 62 per cent there was a preëxisting goiter. The age varied from 20 to 90. Primary malignant tumor gave a worse prognosis than a metastatic growth. Of 82 histologically examined tumors, 46 were carcinoma, 8 proliferating struma of Langerhans, 8 malignant papilloma, 20 sarcoma. The longest duration of life after treatment was instituted was six months; two-thirds of

the patients died within the first four weeks. Surgical removal as well as irradiation exerts very little influence on the prognosis. The earlier statistics gave a very bad prognosis in malignancy of the thyroid. Since 1912, the percentage of survivals beyond the first year has risen in the Breslau clinic from 10 to 46. The improvement is due to earlier operations and to more frequent use of irradiation.

**Tolerance for quinine in exophthalmic goiter.** Bram, I., Arch. Int. Med. **42**: 53-55. 1928.

In 95.6 per cent of patients with exophthalmic goiter, a relative immunity to cinchonism exists; large doses of quinine may be taken with impunity and even with benefit. This is the basis of the quinine diagnostic test for exophthalmic goiter, which is submitted as an asset in the differentiation of this disease from such condtions as affect syndrome, early tuberculosis, neurasthenia and other conditions commonly confused with exophthalmic goiter. In the form of the hydrobromide or the sulphate, quinine is a valuable constituent of the therapeutic armamentarium of the internist who treats patients with exophthalmic goiter, and should be given in the average case in much larger doses than has been the custom.

—Author's Summary.

**The effects of ingestion of thyroid upon the thymus, testicle and thyroid (Action de l'ingestion de corps thyroide sur le thymus sur le testicule et sur la thyroide).** Courrier, R., Rev. franç. d'endocrinol. **6**: 10-48. 1928.

The writer shows by experiment that when white rats are fed fresh thyroid tissue, there is a recession of the thymus when insufficient food is present for maintenance of body weight, but there is no recession if the food supply is adequate. After reviewing work done by others, but apparently without direct experiment, he reaches similar conclusions regarding the testicles. His experiments on the effects on the thyroid gland were carried out on dogs and cats. Similar conclusions were reached, namely, ingestion of thyroid does not produce involution of the thyroid. The opposite effects reported by others he attributes to malnutrition. There is a discussion of the philosophical and clinical significance of his experiments.

—B. Cunningham.

**Effect of desiccated thyroid feeding on growth of the guinea pig.** Durrant, E. P., Am. J. Physiol. **85**: 364. 1928.

Thyroid feeding experiments were made on seven litters of guinea pigs extending from 12 days to 3 months from birth. The dosage was ¼ grain desiccated thyroid (Armour's) on alternate days with some, and the same amount once a week with others. The heavier dosage was followed by the death of the animals in from

12 to 20 days, but all the thyroid-fed animals grew less rapidly than their litter controls; the former showing an increase of weight of 12 per cent to 480 per cent, the latter an increase of from 75 per cent to 675 per cent.—Author's Abst.

**Childhood myxedema.** Gordon, M. B., Am. Med. **23**: 30-36. 1928.

A resume of the present knowledge on the subject is given, and the use of the term "childhood myxedema" is advocated, instead of "sporadic cretinism." The condition which is called sporadic cretinism in this country is not the same condition recognized as cretinism in Europe, and since it differs pathologically and clinically, it should be considered as a separate clinical entity. The condition in America is really an exaggerated and intense form of hypothyroidism. It seems advisable to dispense with the term sporadic cretinism, at least as far as it applies to the condition as it exists in America, and to restrict the term cretinism to the endemic type found in Europe and Asia. Thyroid disorders due to a deficiency in thyroid function are classified according to the following groupings: (1) Endemic cretinism; (2) childhood myxedema (congenital myxedema, infantile myxedema, juvenile myxedema); (3) adult myxedema; (4) post-operative myxedema; (5) hypothyroid states in childhood.

**Psychosis and hyperthyroidism.** Johnson, W. O., J. Nerv. & Ment. Dis. **67**: 558. 1928.

A report is made of observations on 2286 goiter cases operated in the Cleveland Clinic Hospital, 1925-26. A comparison is made between the acute maniacal confusional states of acute thyrotoxicosis and 24 cases of true psychosis. A brief review of the literature is given. The low incidence of true psychosis in thyrotoxic conditions is shown, and it is also shown that in the true psychosis there is personal or family history of psychosis before the goiter develops. Hallucinations and delusions, with predominance of depressive states, is the rule. Operation in these conditions does not cure, in contrast to the thyrotoxic maniacal confusional states. These, if diagnosed and treated before they reach delirium, can be cured.—Author's Abst.